ROLE OF DYSSYNCHRONY ON FUNCTIONAL MITRAL REGURGITATION IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY: A COMPARISON STUDY WITH GEOMETRIC PARAMETERS OF MITRAL APPARATUS

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BACKGROUND: Functional mitral regurgitation (FMR) occurs commonly in patients with dilated cardiomyopathy (DCM). This study was conducted to explore the role of left ventricular (LV) dyssynchrony in developing FMR in patients with DCM in comparison with geometric parameters of the mitral apparatus.

METHODS: Twenty patients without FMR and 33 patients with FMR (effective regurgitant orifice area (ERO) = 0.17 ± 0.10 cm²) were enrolled. MR severity was estimated with ERO area. Dyssynchrony indices (DI) were measured using the standard deviations of time to peak myocardial systolic velocity between eight segments. Using real time 3D echocardiography, mitral valve tenting area (MVTa), anterior (APMD) and posterior papillary muscle distances (PPMD), LV sphericity, and tethering angle of anterior (Aα) and posterior leaflets (Pα) were estimated. All geometrical measurements were corrected (c) by the height of each patient.

RESULTS: The patient with FMR had significantly higher cDI, cMVTa, cAPMD and cPPMD, LV sphericity, Aα, and Pα than the patients without FMR (all p < 0.05). With multiple logistic regression analysis, cMVTa (p = 0.017) found to be strongest predictor of FMR development. In patients with FMR, cMVTa (r = 0.868), cAPMD (r = 0.801), cPPMD (r = 0.742), Aα (r = 0.454), LV sphericity (r = 0.452), and DI (r = 0.410) showed significant correlation with ERO. On multivariate regression analysis, cMVTa and cAPMD (p < 0.001, p = 0.022, respectively) remained the strongest determinants of the degree of ERO and cMVTa and cAPMD (p < 0.001) remained the strongest determinant of the degree of cMVTa.

CONCLUSION: Displacement of anterior papillary muscle and consequent mitral valve tenting seem to play a major role in developing FMR in DCM, while LV dyssynchrony seems to have no significant role.

KEY WORDS: Functional mitral regurgitation · Three dimensional echocardiography · Left ventricular dyssynchrony.
of poor outcome. Recently, cardiac resynchronization therapy (CRT) has emerged as a valuable treatment strategy in drug refractory heart failure patients. Several studies reported that LV dyssynchrony was an independent contributing factor to FMR. But, these studies did not simultaneously investigate geometric changes of LV and mitral apparatus which had been known as the main mechanism of FMR.

The present study was conducted to explore the role of LV dyssynchrony in developing FMR in patients with DCM in comparison with geometric parameters of the mitral apparatus.

**METHODS**

**STUDY POPULATION**

Fifty three consecutive heart failure patients with DCM were enrolled in the study according to the following criteria: impaired LV ejection fraction (EF) ≤ 40%, angiographically no significant luminal narrowing of coronary artery, sinus rhythm, and structurally no abnormality of MV. The patient population was divided into 2 groups: 33 patients (M : F = 15 : 18, age: 58 ± 11 yrs) with FMR (mitral regurgitation (MR) grade ≥ 1), 20 patients (M : F = 14 : 6, age: 64 ± 12 yrs) without FMR.

Exclusion criteria were 1) morphological abnormalities of the mitral apparatus, such as mitral valve prolapse or chordae rupture 2) infiltrative heart disease, congenital heart disease, ischemic heart disease, 3) atrial fibrillation or 4) inadequate 3D echocardiography image due to poor echocardiographic window or patient’s incooperation.

**STUDY METHODS**

**2D ECHOCARDIOGRAPHY**

2D echocardiography was performed with Vivid7 (GE Vingmed, Milwaukee, WI, USA) with 2-4 MHz transducer. Subjects were studied in the left lateral recumbent position. LV volume and function

LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVEDV) were measured by the biplane Simpson’s disk method. LV EF was calculated by the following equation; LV EF = 100 × (LVEDV-LVESV)/LVEDV.

**MR severity**

MR severity was quantified by effective regurgitant orifice area (ERO) by the proximal isovelocity surface area (PISA) method. ERO (cm²) = 6.28 × r² × aliasing velocity/maximal regurgitant flow velocity (r: the radius of isovelocity shell from orifice)

In addition, we estimated MR severity in the patients with two jets by the summation of two jets by PISA.

**LV dyssynchrony**

In the Doppler myocardial image mode, a sample cursor was placed at the midpoint of each of the 8 non-apical segments of the lateral, septal, anterior and inferior walls in the 2 and 4 apical views and myocardial velocity curves were reconstructed. By the adjustment of filter frequency, gain setting, pulse repetition frequency, and color saturation, three consecutive beats were stored and the images were digitized and analyzed (EchoPAC 6.1, GE, Milwaukee, WI, USA). By using the onset of QRS complex as a reference point, the time to peak systolic velocity (Ts) for each of these eight LV segments was measured. Ts was corrected for heart rate using the Bazett’s formula.

Corrected Ts (cTs) = Ts / √R-R [R-R: The time between two consecutive R waves in the ECG (msec)].

The dyssynchrony index (DI) was derived as the standard deviation of the cTs assessed LV segments in each patient.

**REAL-TIME 3D ECHOCARDIOGRAPHY**

Volumetric image acquisition

Using a real time 3D echocardiography (Sonos 7500, Philips Inc., Bothell, WA, USA or Vivid7, GE, Co., Milwaukee, WI, USA), we obtained transthoracic volumetric images with the apical view in all the subjects. The volumetric frame rate was 16 to 22 frames/s, with an imaging depth of 12 to 16 cm. Care was taken to include the entire MV in volumetric data set.

**LV and MV geometry**

We used multi-planar reconstruction (MPR) mode of 3D computer software (4D Cardio-View, Tomtec Co., Munich, Germany) to define the planes for the geometric measurements. First, mid-systole of the heart cycle was defined. Then, a cross-sectional plane of the MV that clearly visualized both mitral commissures was used to define the commissure-commissure (CC) plane, a plane that passes through both commissures and the LV apex. Finally, antero-posterior (AP) planes perpendicular to the center of CC axis was defined for imaging of the geometry of the central side of the MV. The sphericity of LV chamber was calculated by the ratio of the LV chamber width measured at the level of the MV to the height of the level from the mitral annulus on CC plane (Fig. 1).

LV sphericity = LV height / LV width

The degree of leaflet tethering was estimated by measuring the angle at which each leaflet met the annular plane (anterior leaflet: Az, posterior leaflet: Pz) on AP planes (Fig. 1). Mitral annular area (MAA) was then calculated with the simplified equation as below:

MAA = 3.14 × CC dimension × AP dimension / 4

MV tenting area (MVTa), the area enclosed by the annular plane and 2 leaflets was also measured on AP planes (Fig. 1).

**PM distance**

Medial junction of the aortic and mitral annuli (MJAM) was defined as the anatomical reference landmark in measur-
ing degree of PM displacement. After automatic acquisition of the plane that displays all structures (head tips of both PMs and MJAM) together by using MPR mode of 3D image analysis program during midsystole, PM distances (APMD: distance from MJAM to anterior PM head, PPMD: distance from MJAM to posterior PM head, APPMD: distance between anterior and posterior PM head) were measured (Fig. 2). All geometric measurements were corrected (c) by the height of each patient.

Intra-observer variability of PM distance and MR severity
APMD, PPMD, and ERO were measured by one observer and the measurement was repeated by the same observer to check intra-observer variability.

**STATISTICAL ANALYSIS**
Data were analyzed using standard statistical software (Statistical Package for the Social Sciences (SPSS) for windows version 12, SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean and standard deviation and categorical data were expressed as number and percentage. Statistical comparisons of continuous variables between groups were performed by Student’s t-test.

Multiple logistic regression analysis was performed to identify predictors of FMR development. Linear regression analysis and partial correlation tests with Pearson’s method was performed to assess relations of parameters to ERO in the patients with FMR. Stepwise multivariate regression analysis was performed to identify independent factors associated with FMR. A value of p < 0.05 was considered significant.

Intra-observer variability of MPR guided PM distance measurement and ERO calculation with PISA method were tested by calculating Pearson’s correlation coefficient.

**RESULTS**

**BASELINE CHARACTERISTICS**
The mean LV EF was 28 ± 8% in patients with FMR and 29 ± 7% in patients without FMR. There were no differences in the clinical characteristics between two patient groups (Table 1).
The patients with FMR had significantly higher DI (1.43 ± 0.47 vs. 1.12 ± 0.37, \( p < 0.018 \)), cMVTa (1.23 ± 0.40 vs. 0.89 ± 0.19 cm²/m, \( p < 0.001 \)), cAPMD (2.65 ± 0.21 vs. 2.59 ± 0.19 cm/m, \( p < 0.05 \)), cPPMD (2.38 ± 0.22 vs. 2.27 ± 0.18 cm/m, \( p < 0.05 \)), LV sphericity (1.52 ± 0.22 vs. 1.35 ± 0.13, \( p < 0.001 \)), A\( _α \) (35 ± 8° vs. 26 ± 5°, \( p < 0.01 \)), and P\( _α \) (65 ± 10° vs. 56 ± 8°, \( p < 0.01 \)) than the patients without FMR. However, there was no significant differences of cMAA (4.58 ± 0.98 vs. 4.55 ± 1.30 cm²/m, \( p = 0.205 \)) and cAPPMD (1.64 ± 0.24 vs. 1.62 ± 0.43 cm/m, \( p = 0.872 \)) between the 2 patient groups (Table 2).

By multiple logistic regression analysis, cMVTa (\( p = 0.017 \)) was found to be the strongest predictor of FMR development in DCM (Table 3).

**Table 2. Echocardiographic parameters**

| Echocardiographic parameters | FMR (n = 33) | Non-FMR (n = 20) | \( p \) value |
|-----------------------------|-------------|-----------------|-------------|
| ERO (cm²)                   | 0.17 ± 0.10 |                  |             |
| MR grade                    |             |                 |             |
| Mild                        | 19 (58%)    |                 |             |
| Moderate                    | 14 (42%)    |                 |             |
| Severe                      | 0 (0%)      |                 |             |
| cLVEDV (mm³/m)              | 110.4 ± 42.2| 119.7 ± 107.9   | 0.638       |
| cLVESV (mm³/m)              | 80.82 ± 39.51| 70.06 ± 35.58   | 0.324       |
| LV EF (%)                   | 28 ± 8      | 29 ± 7          | 0.616       |
| DI                          | 1.43 ± 0.47 | 1.12 ± 0.37     | 0.018       |
| cMVTa (cm²/m)               | 1.23 ± 0.40 | 0.89 ± 0.19     | < 0.001     |
| cMAA (cm²/m)                | 4.58 ± 0.98 | 4.55 ± 1.30     | 0.205       |
| cPPMD (cm²/m)               | 2.38 ± 0.22 | 2.27 ± 0.18     | 0.014       |
| cAPMD (cm/m)                | 2.65 ± 0.21 | 2.59 ± 0.19     | 0.008       |
| cAPPMD (cm/m)               | 1.64 ± 0.24 | 1.62 ± 0.43     | 0.872       |
| LV sphericity               | 1.52 ± 0.22 | 1.35 ± 0.13     | 0.004       |
| A\( _α \) (°)               | 35 ± 8      | 26 ± 5          | 0.001       |
| P\( _α \) (°)               | 65 ± 10     | 56 ± 8          | 0.002       |

ERO: effective regurgitant orifice, MR: mitral regurgitation, LV: left ventricle, DI: dyssynchrony index, MVTa: mitral valve tenting area, MAA: mitral annular area, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, APPMD: distance between anterior and posterior papillary muscles, L V: left ventricle, A\( _α \): tethering angle of anterior leaflet, P\( _α \): tethering angle of posterior leaflet, c: corrected

**Table 3. Multiple logistic regression analysis for predictors of FMR**

| Odds ratio | 95% CI |
|------------|--------|
| DI         | 1.2    | (0.07-21.16) |
| cMVTa      | 2052.3 | (3.97-1059965.58) |
| cAPMD      | 0.0    | (0.00-1.17) |
| cPPMD      | 1.0    | (0.00-45.60.69) |
| cLV sphericity | 22.2 | (0.04-13012.99) |
| cLVEDV     | 1.0    | (0.90-1.10) |
| A\( _α \)  | 1.1    | (0.90-1.41) |
| P\( _α \)  | 1.0    | (0.86-1.14) |

DI: dysynchrony index, MVTa: mitral valve tenting area, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, LVEDV: left ventricle end diastolic volume, A\( _α \): tethering angle of anterior leaflet, P\( _α \): tethering angle of posterior leaflet, c: corrected

**RELATIONSHIPS OF ECHOCARDIOGRAPHIC PARAMETERS WITH ERO IN PATIENTS WITH FMR**

- cMVTa (\( r = 0.868, p < 0.001 \)), cAPMD (\( r = 0.801, p = 0.005 \)), cPPMD (\( r = 0.742, p = 0.005 \)), \( A_α \) (\( r = 0.454, p = 0.010 \)), LV sphericity (\( r = 0.452, p = 0.016 \)), cLVEDV (\( r = 0.555, p < 0.001 \)), and DI (\( r = 0.410, p = 0.015 \)) showed significant correlation with ERO (Table 4). On the other hand, P\( _α \) (\( r = 0.073, p = 0.698 \)), cMAA (\( r = 0.255, p = 0.125 \)), LV EF (\( r = -0.283, p = 0.111 \)) revealed no significant correlation with ERO (Table 4). By stepwise multivariate regression analysis, cMVTa and cAPMD were found to be the most powerful determinants of ERO (\( R^2 = 0.753, p < 0.001, p = 0.022 \), respectively) (Table 5).

Furthermore, on stepwise multivariate analysis to identify independent factors to determine cMVTa, cAPMD was found to be the strongest determinat of cMVTa (\( R^2 = 0.576, p < 0.001 \)) (Table 6).

**INTRA-OBSERVER VARIABILITY**

The intra-observer correlation coefficients were 0.734 for APMD, 0.698 for PPMD, and 0.952 for ERO (all \( p < 0.001 \)).

**DISCUSSION**

FMR is the result of incomplete mitral leaflet coaptation. MV tenting has been known as the main geometric determinant of FMR but recent studies tended to explain mechanism of FMR by utilizing functional factor such as global or regional dyssynchrony. Soyama et al.\(^ {12} \) reported that dyssynchrony of...
myocardial segments adjacent to the PM may result in discordant coaptation and cause MR in patients with DCM. Donal et al.\textsuperscript{10} reported that LV contractility and dyssynchrony as well as LV geometry and the mitral orifice should be taken into consideration to correctly describe FMR. Vinereanu et al.\textsuperscript{10} explained that CRT reduce FMR by coordinating contraction which leads to an increase in LV longitudinal function, changing the systolic shape of LV and reducing subvalvular traction. Considering improvement of LV systolic function LV and reverse LV remodeling after CRT, the reverse of geometry of the mitral apparatus rather than resynchronization itself may be regarded as the main reason for the improvement of FMR after CRT.\textsuperscript{20-23} Agricola et al.\textsuperscript{11} reported that a larger ERO was associated mainly with excess MV tenting in FMR and regional dyssynchrony was also independently associated with ERO but it has a minor influence. In our results, the geometric parameters, MVT\textsubscript{a} was found to be the main predictor of FMR development in DCM while LV dysynchrony was found to have no significant contribution to it. Moreover, in FMR patients, it was found that MVT\textsubscript{a} was the strongest determinant of MR severity while LV dysynchrony had no significant role in determining MR severity. The results reassured that the geometric parameter of the MV plays the main role in determining MR severity as well as in FMR development in DCM. With respect to the role of LV dyssynchrony, our result was the contrary to the results from several previous studies.\textsuperscript{10-14} Relatively small study population and the inclination of MR severity only to mild and moderate grade in the present study might be the possible reasons for the discrepancy. In addition, most previous studies showing a significant relationship between LV dyssynchrony and FMR assessed regional LV dysynchrony from only 2 segments adjacent to the anterolateral and posteromedial PMs, while the present study assessed global LV dysynchrony from 8 segments.\textsuperscript{12,19} This may be another probable reason for the discrepancy.

While the geometric parameters of the mitral apparatus were estimated by using 2D echocardiography in the past studies,\textsuperscript{19-21} we performed these measurements with combined use of 3D echocardiography and MPR mode for 3D image analysis program in the present study. Taking that accurate measurement with high reproducibility is essential for the geometric measurement of small cardiac structures such as mitral apparatus into account, it is vital to obtain the same planes that cross identical portions of a certain structure, or intersect at a specific angle in every measurement, which is not guaranteed 2D echocardiography. For this reason, geometric measurement of the MV or the tricuspid valve was performed under MPR guide in several previous studies.\textsuperscript{7,24-26} However, it is first trial to estimate the distances of both PMs using MPR in the present study. Using conventional 2D echocardiography, the PM distance was estimated by measuring the distance between the PM head and the contralateral mitral annular point on the apical 2 or 4 chamber plane. However, this method neither guarantees the same plane crossing the identical contralateral annular point in every measurement nor provides two distances of both PMs. In our study, we first defined the PM distance using two anatomical landmarks (the distance from MJAM to the tip of each PM head). The plane displaying the two anatomical landmarks was then obtained using MPR. We expected it would be guaranteed to acquire the identical plane displaying the same point of the PM head in every measurement under MPR guide. However, intra-observer variability of PM distance measurement in the present

| Table 4. Correlations of ERO with other parameters |
|-----------------|------|------|
| R   | p value |
|------|--------|
| DI   | 0.400 | 0.015 |
| cMVT\textsubscript{a} | 0.868 | < 0.001 |
| cMAA | 0.235 | 0.125 |
| cPPMD | 0.742 | 0.005 |
| cAPMD | 0.801 | 0.005 |
| LV sphericity | 0.432 | 0.016 |
| \(A_{\alpha}\) | 0.434 | 0.010 |
| \(P_{A}\) | 0.073 | 0.698 |
| LV EF | -0.283 | 0.111 |
| cLVEDV | 0.535 | 0.001 |

ERO: effective regurgitant orifice area, DI: dyssynchrony index, MVT\textsubscript{a}: mitral valve tenting area, MAA: mitral annular area, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, LV: left ventricle, \(A_{\alpha}\): tethering angle of anterior leaflet, \(P_{A}\): tethering angle of posterior leaflet, LV EF: left ventricle ejection fraction, LVEDV: left ventricle end diastolic volume, c: corrected

| Table 5. Stepwise multivariate regression analysis for determinants of ERO |
|-----------------|-----------------|-----------------|-----------------|
|                  | DI and LV geometric parameters | DI and MVT\textsubscript{a} geometric parameters | Including all parameters |
|                  | R    | SE  | R    | SE  | R    | SE  |
| DI               | 0.164 | 0.605 | 0.400 | 0.015 | 0.605 | 0.015 |
| Sphericity       | 0.076 | 0.423 | 0.004 | 0.277 |
| cLVEDV           |       |       | 0.686 | 0.686 |
| cAPMD            |       |       | 0.665 | 0.665 |
| cPPMD            |       |       | 0.022 | 0.022 |
| cMVT\textsubscript{a} | < 0.001 | < 0.001 |
| R\textsuperscript{2} | 0.275 | 0.807 | 0.807 |

ERO: effective regurgitant orifice area, DI: dyssynchrony index, LVEDV: left ventricle end diastolic volume, \(A_{\alpha}\): tethering angle of anterior leaflet, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, MVT\textsubscript{a}: mitral valve tenting area, c: corrected

| Table 6. Stepwise multivariate regression analysis for determinant of cMVT\textsubscript{a} |
|-----------------|-----------------|-----------------|
|                  | \(\beta\) | SE  | p value |
|                  |       |      |        |
| cAPMD            | 1.435 | 0.207 | < 0.001 |

MVT\textsubscript{a}: mitral valve tenting area, SE: standard error, APMD: anterior papillary muscle distance, c: corrected
study was less satisfactory than we expected. It was probably due to the cone shape of the PM head. The PM head displayed in any cut plane always had the tip because of its appearance of triangle. Therefore, it was a little perplexing to identify the same tip of the PM head repeatedly even under MPR guide. However, the reproducibility is expected to improve after certain period of time of learning curve.

**STUDY LIMITATIONS**

In the present study, first, the study population was relatively small and the MR grade leaned to the mild to moderate MR. These might affect the results of the present study.

Therefore, further investigations in larger population with more diverse degrees of MR and needed. Second, we assessed LV dysynchrony from 8 segments of LV not 12 segments of LV. Third, we estimated MR severity without accounting the loading conditions that would modulate geometry of the LV and the mitral apparatus. Fourth, 3D echocardiography has several limitations, which are low temporal and spatial image resolution and inability to transfer electrocardiography to the off-line image analysis program. Fifth, we assessed MR severity using PISA method that assumed the geometry of PISA to be hemispherical shape. However, with development of 3D color flow imaging, PISA particularly in FMR has been found to be hemiellipsoidal shape, which suggested that MR severity might be underestimated by conventional PISA method. 22-24

In conclusion, mitral valve tenting secondary to PM, in particular, anterior PM displacement that is identified as the most important geometric determinant of MV tenting area seems to play a main role in developing FMR and determining its severity in DCM. On the other hand, LV dysynchrony does not seem to have significant role in the mechanism of FMR in DCM.

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REFERENCES

1. Blondheim DS, Jacobs LE, Koter MN, Costacurta GA, Parry WR. Dilated cardiomyopathy with mitral regurgitation: deemed survival despite a low frequency of left ventricular thrombus. Am Heart J 1991;122:763-71.

2. Tahrat SA, Oury JH, Maxwell JM, Hiro SP, Duran GM. Outcome after mitral valve repair for functional ischemic mitral regurgitation. J Heart Valves Dis 2002;11:11-18; discussion 18-9.

3. Tomita T, Nakatani S, Eishi K, Takeda M, Takasawa A, Koyanagi H, Kameda Y, Kitamura S, Komamura K, Yasumura Y, Yamagishi ZB, Qin JX, Gillinov MA, Levine RA. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vitro demonstration of altered leaflet tethering geometry. Circulation 1997;96:1999-2008.

4. Otsuji Y, Handschumacher MD, Schwammenthal E, Jiang L, Song JK, Guerrero JL, Vilahakes GJ, Levine RA. Mechanism of ischemic mitral regurgitation with segmental left ventricular dysfunction: three-dimensional echocardiographic studies in models of acute and chronic progressive regurgitation. J Am Coll Cardiol 2001;37:641-8.

5. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determination of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation 2000;102:1400-6.

6. Kwon J, Shin T, Agler DA, Popovóv ZB, Qin JX, Gillinov MA, Stewart WJ, Congrove DM, McCarthy PM, Thomas JD. Real-time three-dimensional echocardiography study. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation: real-time three-dimensional echocardiography study. Circulation 2003;107:1135-40.

7. Linde C, Braunschweig F, Gaedler F, Bailleul C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). Am J Cardiol 2003;91:1090-5.

8. Erlebacher JA, Barzazah S. Intraventricular conduction delay and functional mitral regurgitation. Am J Cardiol 2001;88:A7, 83-6.

9. Pietra LA. Left ventricular dyssynchrony and functional mitral regurgitation: two dynamic conditions. Eur Heart J 2007;28:924-5.

10. Agricola E, Oppizzi M, Gaiardi S, Misani M, Meris A, Papponc B, Margonato A. Role of regional mechanical dyssynchrony as a determinant of functional mitral regurgitation in patients with left ventricular systolic dysfunction. Heart 2006;92:1390-5.

11. Soyama A, Kono T, Shimizu T, Motita H, Ito T, Sumi W, Kitaura Y. Intraventricular dyssynchrony may play a role in the development of mitral regurgitation in dilated cardiomyopathy. J Card Fail 2005;11:631-7.

12. Ennezat P, Turnier MS, Beadle RA, Mumford CE,CNTreza M, Frenneaux MP, Frater AG. Mechanisms of reduction of mitral regurgitation by cardiac resynchronization therapy. J Am Soc Echocardiogr 2007;20:54-62.

13. Ennezat PV, Maréchaux S, Le Tourneau T, Lamblin N, Bausters C, Van Belle E, Gal B, Kacet S, Asseman P, Deklunder G, LeJemtel TH, de Groote P. Myocardial synchrony is a determinant of changes in functional mitral regurgitation severity during dynamic exercise in patients with chronic heart failure due to severe left ventricular systolic dysfunction. Eur Heart J 2006;27:679-83.

14. Schiller NH, Shah PM, Crawford M, DeMaria A, Devereux R, Figenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358-77.

15. Linde C, Braunschweig F, Gaedler F, Bailleul C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). Am J Cardiol 2003;91:1090-5.

16. Enriquez-Sarano M, Seward JB, Bailey KR, Tajik AJ. Effective regurgitant orifice area: a nomogram Doppler development of an old hemodynamic concept. J Am Coll Cardiol 1994;23:443-51.

17. Watanabe N, Ogasawara Y, Yamaura Y, Yamamoto K, Wada N, Kawamoto T, Toyora E, Akasaka T, Yoshida K. Geometric differences of the mitral valve tenting between anterior and inferior myocardial infarction with significant ischemic mitral regurgitation: quantitation by novel software system with transaxial real-time three-dimensional echocardiography. J Am Soc Echocardiogr 2006;19:71-5.

18. Chatterpadhyay S, Alam MF, Nikitin NP, Frauser AG, Clark AL, Cleland JG. The effect of pharmacological stress on intraventricular dysynchrony in left ventricular systolic dysfunction. Eur J Heart Fail 2006;8:412-20.

19. Donal E, De Place C, Kervio G, Bauser E, Gervais R, Lesler C, Malo P, Daubert JC. Mitral regurgitation in dilated cardiomyopathy.
value of both regional left ventricular contractility and dyssynchrony. Eur J Echocardiogr 2009;10:133-8.

20. Breithardt OA, Sinha AM, Schwanerenthal E, Bislaoui N, Markus KU, Franke A, Stellbrink C. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003;41:765-70.

21. Kanzaki H, Bazaz R, Schwartzman D, Dahi K, Sade LE, Gorcsan J 3rd. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. J Am Coll Cardiol 2004;44:1619-25.

22. Ypenburg C, Lancellotti P, Tops LF, Boersma E, Bleeker GB, Holman ER, Thomas JD, Schali MJ, Pérard LA, Bax JJ. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. Eur Heart J 2008;29:757-65.

23. Linde C, Leclercq C, Rex S, Gattigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111-8.

24. 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 2007;8:195-203.

25. Song JM, Qin JX, Kongasarrepong V, Shiota M, Agler DA, Smedira NG, McCarthy PM, Marc Gillinov A, Thomas JD, Shiota T. Determinants of ischemic mitral regurgitation in patients with chronic anterior wall myocardial infarction: a real time three-dimensional echocardiography study. Echocardiography 2006;23:650-7.

26. Min SY, Song JM, Kim JH, Jang MK, Kim YJ, Song H, Kim DH, Lee JW, Kang DH, Song JK. Geometric changes after tricuspid annuloplasty and predictors of residual tricuspid regurgitation: a real-time three-dimensional echocardiography study. Eur Heart J 2010;31:2871-80.

27. Matsumura Y, Fukuoka T, Tran H, Greenberg NL, Agler DA, Wada N, Toyono M, Thomas JD, Shiota T. Geometry of the proximal continuity surface area in mitral regurgitation by 3-dimensional color Doppler echocardiography: difference between functional mitral regurgitation and prolapse regurgitation. Am Heart J 2008;155:231-8.

28. Yosefy C, Levine RA, Solis J, Vaturi M, Handschumacher MD, Hung J. Proximal flow convergence region as assessed by real-time 3-dimensional echocardiography: challenging the hemispheric assumption. J Am Soc Echocardiogr 2007;20:389-96.