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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 cm^2] 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 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.

Introduction

Functional mitral regurgitation (FMR), which occurs as consequence of regional or left ventricular (LV) dysfunction despite a structurally normal mitral valve (MV), is common complication in patients with ischemic heart disease or idiopathic dilated cardiomyopathy (DCM). Its presence is considered to be a significant risk factor for worse outcome.[1-3]

Development of FMR and its severity have been attributed to geometric changes of the MV apparatus such as papillary muscle (PM) displacement due to LV global or regional remodeling, MV tethering or tenting, reduced closing force and dilatation of mitral annulus.[4-7]

LV dyssynchrony is a frequently observed feature in patients with heart failure, and is recognized as an important predictor

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of poor outcome. Recently, cardiac resynchronization therapy (CRT) has emerged as a valuable treatment strategy in drug refractory heart failure patients.[8] Several studies reported that LV dyssynchrony was an independent contributing factor to FMR.[9-14] 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%, angiophically 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 (LVESV) were measured by the biplane Simpson's disk method.[15] 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.[16]

ERO (cm^2) = 6.28 × r^2 × 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.[17]

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 reconstituted. By the adjustment of filter frequencty, 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.[18]

Correted 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-poserior (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: Aα, posterior leaflet: Pα) 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 anatominal reference landmark in measur-

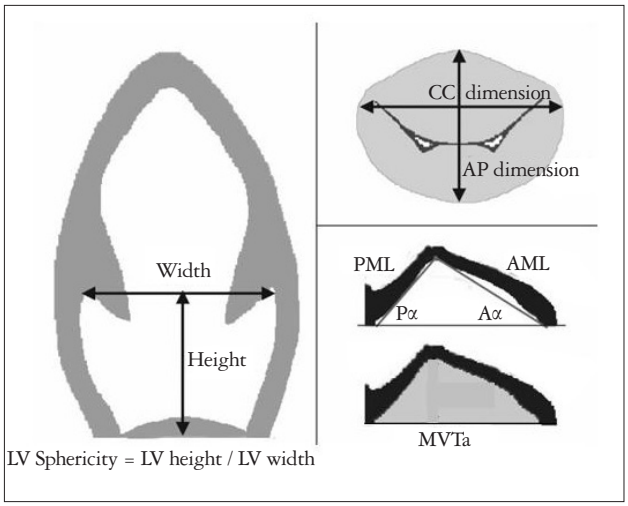

Fig. 1. Schematic illustrations explaining geometric parameters of the left ventricle (left) and the mitral apparatus (right). LV: left ventricle, AML: anterior mitral leaflet, PML: posterior mitral leaflet, AP: antero-posterior, CC: commissure-commissure, Aα: tethering angle of anterior leaflet, Pα: tethering angle of posterior leaflet, MVTa: mitral valve tenting area.

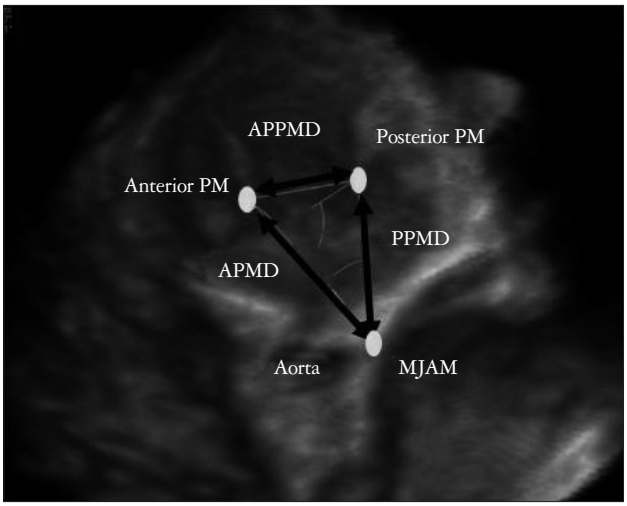

Fig. 2. The distance between the MJAM and the head of each PM was defined as the PM distance. PM: papillary muscle, MJAM: medial junction of the aortic and mitral annuli, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, APPMD: distance between anterior and posterior papillary muscles.

Table 1. Clinical characteristics of the study population

	FMR (n = 33)	Non-FMR (n = 20)	*p* value
Age (yrs)	64 ± 12	58 ± 11	0.068
Sex (M/F)	15/18	14/6	0.080
QRS duration (ms)	117 ± 27	113 ± 27	0.817
DM (%)	6 (18)	5 (25)	0.728
HTN (%)	7 (21)	7 (35)	0.270
LBBB (%)	6 (18)	1 (5)	0.176
ACE inhibitor (%)	32 (96)	17 (90)	0.273
Beta blocker (%)	16 (48)	11 (55)	0.523

FMR: functional mitral regurgitation, DM: diabetes mellitus, HTN: hypertension, LBBB: left bundle branch block, ACE: angiotensin converting enzyme

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).

Table 2. Echocardiographic parameters

	FMR (n = 33)	Non-FMR (n = 20)	*p* value
ERO (cm^2)	0.17 ± 0.10		-
MR grade			
Mild	19 (58%)		
Moderate	14 (42%)		
Severe	0 (0%)		
cLVEDV (mm^3/m)	110.4 ± 42.2	119.7 ± 107.9	0.638
cLVESV (mm^3/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 (cm^2/m)	1.23 ± 0.40	0.89 ± 0.19	< 0.001
cMAA (cm^2/m)	4.58 ± 0.98	4.55 ± 1.30	0.205
cPPMD (cm/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
Aα (°)	35 ± 8	26 ± 5	0.001
Pα (°)	65 ± 10	56 ± 8	0.002

ERO: effective regurgitant orifice, MR: mitral regurgitation, LVEDV: left ventricle end diastolic, LV EF: left ventricle ejection fraction, 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, LV: left ventricle, Aα: tethering angle of anterior leaflet, Pα: 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	(0.00-45360.69)
LV sphericity	22.2	(0.04-13012.99)
cLVEDV	1.0	(0.99-1.01)
Aα	1.1	(0.90-1.41)
Pα	1.0	(0.86-1.14)

DI: dyssynchrony index, MVTa: mitral valve tenting area, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, LVEDV: left ventricle end diastolic volume, Aα: tethering angle of anterior leaflet, Pα: tethering angle of posterior leaflet, c: corrected

ECHOCARDIOGRAPHIC PARAMETERS BETWEEN TWO PATIENTS GROUPS

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 cm^2/m, $p < 0.005$), 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, $p < 0.005$), Aα (35 ± 8° vs. 26 ± 5°, $p < 0.01$), and Pα (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 cm^2/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).

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 ($r = 0.742$, $p = 0.005$), Aα ($r = 0.454$, $p = 0.010$), 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, Pα ($r = 0.073$, $p = 0.698$), 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.[19] 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.[13] 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.[20-23] Agricola et al.[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, MVTa was found to be the main predictor of FMR development in DCM while LV dyssynchrony was found to have no significant contribution to it. Moreover, in FMR patients, it was found that MVTa was the strongest determinant of MR severity while LV dyssynchrony 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.[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 dyssynchrony from only 2 segments adjacent to the anterolateral and posteromedial PMs, while the present study assessed global LV dyssynchrony from 8 segments.[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,[18-21] 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.[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
cMVTa	0.868	< 0.001
cMAA	0.255	0.125
cPPMD	0.742	0.005
cAPMD	0.801	0.005
LV sphericity	0.452	0.016
Aα	0.454	0.010
Pα	0.073	0.698
LV EF	-0.283	0.111
cLVEDV	0.555	0.001

ERO: effective regurgitant orifice area, DI: dyssynchrony index, MVTa: mitral valve tenting area, MAA: mitral annular area, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, LV: left ventricular, Aα: tethering angle of anterior leaflet, Pα: 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 MV geometric parameters	Including all parameters
DI	0.164	0.605	0.605
Sphericity	0.076		0.423
cLVEDV	0.004		0.277
Aα		0.686	0.686
cPPMD		0.665	0.665
cAPMD		0.022	0.022
cMVTa		< 0.001	< 0.001
R^2	0.275	0.807	0.807

ERO: effective regurgitant orifice area, DI: dyssynchrony index, LVEDV: left ventricle end diastolic volume, Aα: tethering angle of anterior leaflet, PPMD: posterior papillary muscle distance, APMD: anterior papillary muscle distance, MVTa: mitral valve tenting area, c: corrected

Table 6. Stepwise multivariate regression analysis for determinant of cMVTa

	β	SE	*p* value
cAPMD	1.435	0.207	< 0.001

MVTa: 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 dyssynchrony 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. [27)28)]

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 dyssynchrony does not seem to have significant role in the mechanism of FMR in DCM.

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