The mechanisms of functional mitral regurgitation in patients with dilated cardiomyopathy: a real-time 3D echocardiographic study

Noriko OKAHASHI[1)], Randolph P. MARTIN[2)], Andreas P. KALOGEROPOULOS[2)]
Stamatios LERAKIS[2)], Maria-Alexandra PERNETZ[2)], Miwako TSUKIJI[3)]
Yasuko YAMAURA[1)], Nozomi WATANABE[1)], Hiroyuki OKURA[1)]
Kiyoshi YOSHIDA[1)]

1) Department of Cardiology, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan
2) Division of Cardiology, Emory University Hospital, 1364 Clifton Rd., D-433, Atlanta, GA, 30322, U.S.A.
3) Division of Cardiology, New Tokyo Hospital, 473-1 Nemoto, Matsudo, 271-0077, Japan

ABSTRACT Functional mitral regurgitation (FMR) conveys an adverse prognosis in dilated cardiomyopathy (DCM). Although incomplete closure of the normal leaflet is the immediate cause of FMR, the link between left ventricular (LV) geometry and the degree of mitral regurgitation (MR) is not well defined. The purpose of this study was to evaluate the mitral complex and the LV geometry, and to clarify the mechanisms of FMR in patients with DCM by using real-time 3D echocardiography. In this study we examined 36 DCM patients. These patients were divided into two groups according to MR volume [group 1: mild (<30ml), group 2: moderate to severe (≥30ml)]. By using a novel valve software system (REALVIEW®), mitral apparatus geometry including annular size, tenting length and volume, coaptation index, tethering length, interpapillary distance and angle were quantitatively analyzed. The LV geometry was evaluated by measuring the following diameters from 3D volumetric data (QLAB™): LV longitudinal diameter, LV anterior-posterior (AP) diameter, LV medial-lateral (ML) diameter and ML/AP ratio. Patients in group 2 had a larger annular size, apparent leaflet tenting and longer distance from papillary muscle to mitral annulus (tethering length) compared to the patients in group 1. In DCM patients with moderate to severe MR, the LV ML diameter and the ML/AP ratio is higher compared to patients with mild MR due to a LV deformity. This laterally dilated LV results in the loss of coaptation, aggravating FMR in patients with DCM.

(Accepted on September 10, 2010)

Key words：**3D echocardiopraphy, Functional mitral reguragitation, Dilated cardiomyopathy**

INTRODUCTION

Functional mitral regurgitation (FMR) occurs as a consequence of regional or global left ventricular (LV) dysfunction despite a structurally normal

Corresponding author
Noriko Okahashi
Department of Cardiology, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan
Phone : 81 86 462 1111
Fax : 81 86 462 1199
E-mail : okahashi@med.kawasaki-m.ac.jp

mitral valve, it is widely recognized that FMR development in ischemic or non-ischemic dilated cardiomyopathy (DCM) predicts a poor clinical outcome[1-4]. Optimal repair of FMR requires an understanding of its mechanisms. Therefore, the use of multiple echocardiographic parameters to assess FMR severity and its major mechanism for planning therapeutic options may be expedient. Recent two-dimensional (2D) and three-dimensional (3D) studies have examined the mechanisms of FMR. Global LV dilation and sphericity have been implicated in FMR by altering the mitral annulus and subvalvular apparatus, and ultimately causing an incomplete coaptation. However, in clinical practice, FMR varies widely despite the same degree of LV dysfunction. A three-dimensional evaluation of the LV shape and mitral geometry might help in the assessment of the mechanisms of FMR. Recently, we have successfully quantified the geometry of the mitral valve apparatus using a custom software system with 3D echocardiography (REALVIEW®). We reported that the bulging mitral leaflets are tethered to the LV and the coaptation index was reduced in FMR with LV dysfunction[5-10]. In this study, we sought to elucidate the mechanisms of FMR from the view of geometrical changes in the mitral apparatus and the LV by using REALVIEW® on real-time 3D transthoracic echocardiography.

MATERIALS AND METHODS

Patient Population

Thirty-six patients with chronic LV systolic dysfunction were recruited for a 3D echocariographic examination (age 60 ± 18 years, 21 men / 15 women). The patients were divided into 2 groups according to the mitral regurgitation (MR)volume [group 1: mild, < 30ml; group 2: moderate to severe, ≥ 30ml]. Exclusion criteria were: (1) organic mitral valve or subvalvular lesion (eg. mitral leaflet prolapse or rheumatic disease), (2) other cardiac diseases (eg. ischemic, pericardial, congenital or infiltrative heart disease) and (3) arrythmia (eg. atrial fiblilation). The study protocol was approved by the institutional review board, and all subjects gave written informed consent.

Echocardiographic Protocol

All the echocardiographic examinations were performed using commercially available cardiovascular ultrasound systems (SONOS iE33® with S3 and X3-1 probe, Philips Medical Systems, Bothell, WA, or Vivid 7® with M3S and M4S probes, GE Healthcare, Milwaukee, WI). The acquired images were transferred to a dedicated workstation for offline analysis via network.

Two-dimensional Echocardiographic Study

All patients underwent a standard 2D echocardiographic examination. Left ventricular dimensions and the left atrial diameter were measured in the parasternal long axis view. Mitral regurgitation was evaluated by color Doppler echocardiography, and the degree of MR was quantified by regurgitant orifice area (ROA) and MR volume using the PISA method. When MR degree was nil or trivial as assessed by color Doppler, the MR volume and ROA were assumed to be null.

Three-dimensional Echocardiographic Study

< Volumetric Image Acquisition >

Utilizing a real-time 3D echocardiographic system, transthoracic volumetric images (full-volume mode) from the apical view were obtained from all subjects. The volumetric frame rate was 11 to 18 frames / second, with an imaging depth of 14 to 18 cm. We carefully adjusted the transducer to be located at the apex in bi-plane mode before acquiring a full-volume image. All volumetric images were digitally stored and transferred to a computer for offline analysis.

< 3D image reconstruction >

We used a novel 3D computer software, REALVIEW ® (Y.D., Ltd, Osaka, Japan) to analyze the volumetric images. Based on previous studies [5－10], the 3D volumetric data were automatically cropped into 18 radial planes spaced 10 degrees apart. The mitral annulus was manually marked and the mitral leaflets were semi-automatically traced in each cropped plane in mid-systole. The tips of the anterolateral and the posteromedial papillary muscles were obtained and marked on the cropped planes also. From these data, anatomic 3D images of the mitral valve apparatus were reconstructed for quantitative measurements (Fig. 1).

< 3D morphology of mitral complex>

As previously described [5－10], mitral annular area, circumference, tenting length, tenting volume and the 3D tenting surface area were measured for the evaluation of the mitral leaflet geometry. The coaptation index was calculated to evaluate the degree of leaflet coaptation. To evaluate a shift in the papillary muscle position, the distance from anterior mitral annulus to the tips of the papillary muscle (tethering lengths) and the angle between the two lines connecting the anterior mitral annulus to each papillary muscle (interpapillary angle) were also measured.

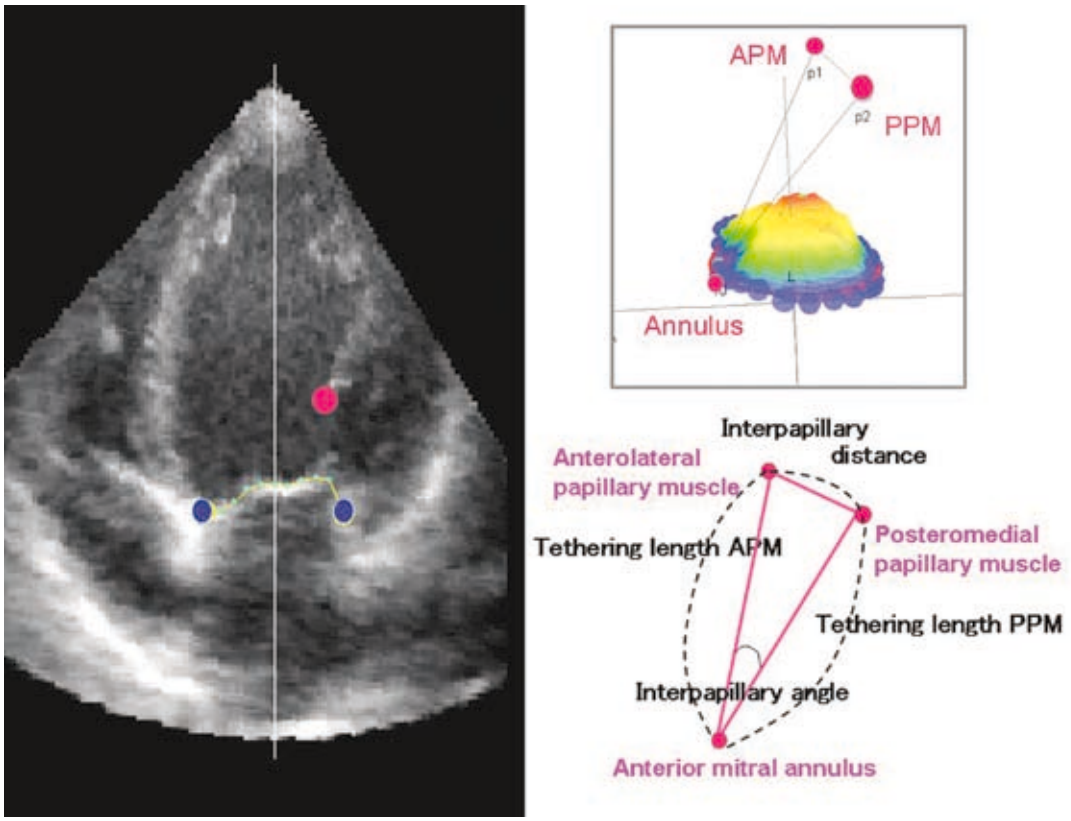

Fig. 1. The reconstruction of 3D images of the mitral complex
The 3D volumetric image was automatically cropped into 18 equally spaced radial planes. The mitral annulus and the leaflets were traced in each cropped plane. The tips of the papillary muscles were marked (left). From these points, 3D images of the mitral leaflets and the annulus were reconstructed accounting for the position of the two papillary tips (upper right). Measurements of the interpapillary distance, the interpapillary angle and the tethering lengths between the anterior mitral annulus to the anterolateral papillary muscle (Tethering length APM) and to the posteromedial papillary muscle (Tethering length PPM) are schematically shown (lower right).
APM: anterolateral papillary muscle, PPM: posteromedial papillary muscle

< 3D measurement of LV >

All patients underwent 3D echocardiographic examinations. The LV end-diastolic volume (LVEDV) and the LV end-systolic volume (LVESV) were measured with 3D quantitation software (QLAB™, Philips Ultrasound, Bothell, WA). Ejection fraction (EF, %) was calculated as 100 x (LVEDV-LVESV)/LVEDV. The LV geometry was evaluated by measuring the following diameters from 3D volumetric data in mid systole (Fig. 2): in the short LV axis view at the level of the papillary muscle tips, we measured the anterior-posterior diameter (LV AP diameter) and the medio-lateral diameter (LV ML diameter). In the longitudinal LV axis, the distance from the apex to the mitral annulus level was recorded to measure the LV longitudinal diameter.

Statistical Analysis

Data are expressed as the mean value ± SD. The comparisons between groups were performed with a Student's t test. A p-value < 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics and echocardiographic measurements are summarized in the Table 1. There were 18 patients in each group. There was no

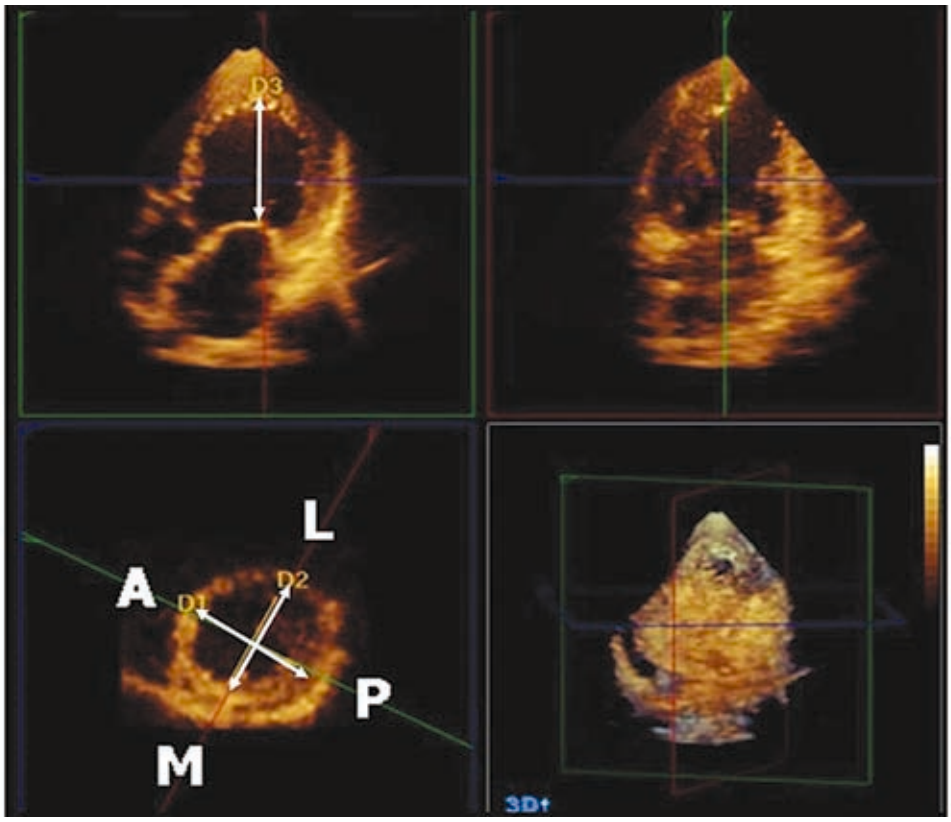

Fig. 2. 3D measurements of the LV geometry
The LV geometry was measured at end systole in 3D volumetric images. The height of the LV was calculated as the longest distance between the center of the mitral annulus and the endocardial apex (upper panels). The LV width was calculated at the level of the papillary muscles (lower right panel).
A: anterior, P: posterior, M: medial, L: lateral

difference in age, gender, or LV chamber diameters between the two groups.

Mitral complex geometry

The annular area, tenting length and tenting volume in group 2 were larger and the coaptation Index was significantly smaller than of those in group 1 (Annular area, 6.8 ± 1. cm^2/m^2 vs. 55.8 ± 1.0 cm^2/m^2, p=0.016; Tenting length, 4.7 ± 1.8 mm/m^2 vs. 3.4 ± 1.7mm/m^2, p=0.040; Tenting volume, 4.1 ± 1.5 ml/m^2 vs. 2.7 ± 1.3ml/m^2, p=0.005; Coaptation index, 8.8 ± 2.1% vs. 16.4 ± 5.8%, p<0.001). Both distances, from the anterior annulus to the anterolateral papillary muscle (Tethering length-APM) and the posteromedial papillary muscle (Tethering length-PPM) were also longer in group 2 (26.7 ± 3.8 mm/m^2 vs. 23.2 ± 4.4 mm/m^2, p=0.018; 27.8 ± 4.4 mm/m^2 vs. 24.1 ± 3.2 mm/m^2, p=0.009).

In the LV deformity indices, the LV ML diameter in group 2 was significantly longer than of those that in group 1 (3.9 ± 0.7 mm/m^2 vs. 3.4 ± 0.3 mm/m^2, p=0.004). There were no differences, however, in the LV AP diameter or the LV longitudinal diameter between the two groups (3.5 ± 0.5 mm/m^2 vs. 3.3 ± 0.4 mm/m^2, p=0.304; 5.0 ± 0.7 mm/m^2 vs. 5.1 ± 0.5 mm/m^2, p=0.698). The ML/AP ratio in group 2 was higher than that of group 1 (1.13 ± 0.13 vs.1.05 ± 0.08, p=0.002). These geometry changes of the LV were significantly correlated with the degree of MR (Fig. 3).

DISCUSSION

In the present study, the LV lateral diameter was larger in patients with moderate-to-severe MR (<30ml) compared to those with mild MR (<30ml), although the LV diameter and volume/EF did

Table 1. Baseline characteristics and echocardiographic parameters

Variable	Mild MR (n=18)	Mod/Severe MR (n=18)	P value
Age, years	53 ± 19	64 ± 16	N.S.
Gender, male n (%)	11 (61)	10 (55)	N.S.
2D Echocardiography			
LV diameter diastolic, mm/m^2	36 ± 5	38 ± 7	0.302
LV diameter systolic, mm/m^2	32 ± 5	33 ± 7	0.519
LA diameter, mm/m^2	25 ± 4	29 ± 5	0.18
MR volume, ml/m^2	14 ± 9	54 ± 11	<0.001
3D Echocardiography			
-Mitral valve geometry			
Annular area, cm^2/m^2	5.8 ± 1.0	6.8 ± 1.5	0.016
Annular circumference, cm/m^2	6.7 ± 0.7	7.4 ± 1.1	0.046
Tenting length, mm/m^2	6.4 ± 2.3	8.3 ± 2.2	0.017
Tenting volume, ml/m^2	2.7 ± 1.3	4.1 ± 1.5	0.005
Coaptation index	16.4 ± 5.8	8.8 ± 2.1	<0.001
-Papillary muscle position			
Tethering length PPM, mm/m^2	24.1 ± 3.2	27.8 ± 4.4	0.009
Tethering length APM, mm/m^2	23.2 ± 4.4	26.7 ± 3.8	0.018
Interpapillary distance, mm/m^2	16 ± 3	17 ± 4	0.619
Interpapillary angle, degree	40 ± 12	34 ± 10	0.164
-Left ventricular chamber			
LV end-diastolic volume, ml/m^2	88 ± 29	112 ± 42	0.055
LV end- systolic volume, ml/m^2	63 ± 27	86 ± 39	0.053
LV ejection fraction, %	29 ± 8	25 ± 7	0.069
-Left ventricular deformity			
LV longitudinal diameter, cm/m^2	5.0 ± 0.7	5.1 ± 0.5	0.698
LV AP diameter, cm/m^2	3.3 ± 0.4	3.5 ± 0.5	0.304
LV ML diameter, cm/m^2	3.4 ± 0.3	3.9 ± 0.7	0.004
LV ML/AP ratio	1.05 ± 0.08	1.13 ± 0.13	0.002

2D: two-dimensional, 3D: three-dimensional, LV: left ventricular, LA: left atrium,
MR: mitral regurgitation, PPM: posterior papillary muscle, APM: anterior papillary muscle, AP: anterior-posterior, ML: medial-lateral,

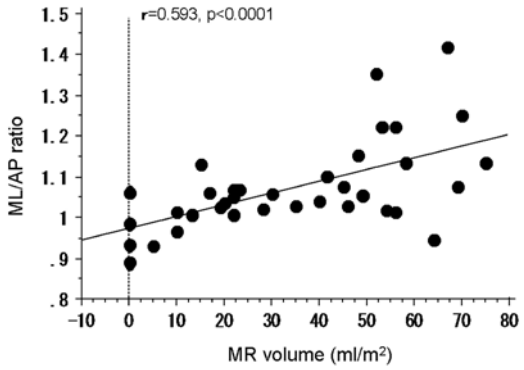

Fig. 3. The relationship between the degree of MR and the LV geometry measured by 3D echocardiography in DCM
ML/AP ratio was significantly correlated with MR severity ($r = 0.593$, $p < 0.0001$).

not show significant differences between the two groups.

In patients with LV dysfunction and dilation, the leaflets are usually tethered by the outward displacement of the LV wall and the papillary muscles[11−13]. The papillary muscles, which are normally parallel to the LV long axis, become displaced as a result of ischemia or heart failure, drawing the leaflet toward the ventricle and restricting its motion against closure[4, 13]. In such conditions, the coaptated leaflet area would be decreased and the degree of mitral valve leaflet coaptation should be an important parameter in the assessment of FMR. The present study demonstrated that mitral leaflets were more globally bulged into the LV with a loss of coaptation. Furthermore the tethering lengths in both the anterolateral papillary muscle and the posteromedial papillary muscle directions were longer in the moderate-to-severe MR group.

The remodeling of the normally ellipsoid LV to a more spherical chamber is observed in DCM[14, 15]. The extent of LV shape abnormality was evaluated with a sphericity index (the ratio of the major axis to minor axis of the LV) using a 2D echocardiography in previous studies. In our study, we measured the diameters of the longitudinal direction (LV longitudinal diameter), the anterior to posterior direction (LV AP diameter) and the medial to lateral direction (LV ML diameter) to perform a 3D evaluation of the extent of the LV shape deformation. In our study, indices of the global LV dilatation and dysfunction such as the LV size, volume and EF demonstrated no significant differences in DCM with either mild or moderate-to-severe MR. In contrast, the LV ML diameter and the ML/AP ratio were greater in patients with moderate-to-severe MR. In addition, the ML/AP ratio was strongly correlated with MR severity and coaptation index. These results may explain the geometric changes of the LV causing MR; specifically, the displacement of the papillary muscles to the postero-lateral direction may impair leaflet coaptation and cause FMR.

STUDY LIMITATIONS

This study has several limitations. First, the quality of real-time 3D echocardiography images currently acquired in a clinical setting is lower than that of conventional 2D echocardiography. Because the software system used in the present study requires identification of the mitral annulus and the tip of the papillary muscles for tracing, technically inadequate real-time 3D echocardiographic images are not amenable to analysis. Second, this method is based on the hypothesis that the mitral leaflets closure is almost symmetric in patients with DCM. Another approach should be considered in differing conditions, such as an apparent detachment or a gap in the tips of the leaflets during systole.

CONCLUSIONS

In DCM patients with moderate-to-severe MR ($\geq$ 30ml), the LV ML diameter and the ML/AP ratio are increased due to an exaggerated LV deformity compared to patients with mild MR (<30ml). Thus,

a laterally dilated LV results in a loss of coaptation, aggravating FMR in patients with DCM.

REFERENCES

1) 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 83 : 14-20, 1993

2) Blondheim DS, Jacobs LE, Kotler MN, Costacurta GA, Parry WR : Dilated cardiomyopathy with mitral regurgitation: decreased survival despite a low frequency of left ventricular thrombus. Am Heart J 122 : 763-771,1991

3) Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ : Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 103 : 1759-1764, 2001

4) Levine RA, Schwammenthal E : Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. Circulation 112 : 745-758, 2005

5) Yamaura Y, Watanabe N, Ogasawara Y, Wada N, Kawamoto T, Akasaka T, Yoshida K : Geometrical demonstration and three-dimensional quantitative analysis of the mitral valve with real-time three-dimensional echocardiography: novel anatomical image creation system. J Echocardiogr 2 : 99-104, 2004

6) Watanabe N, Ogasawara Y, Yamaura Y, Kawamoto T, Toyota E, Akasaka T, Yoshida K : Quantitation of mitral valve tenting in ischemic mitral regurgitation by transthoracic real-time three-dimensional echocardiography. J Am Coll Cardiol 45 : 763-769, 2005

7) Watanabe N, Ogasawara Y, Yamaura Y, Kawamoto T, Akasaka T, Yoshida K : Geometric deformity of the mitral annulus in patients with ischemic mitral regurgitation: a real-time three-dimensional echocardiographic study. J Heart Valve Dis 14 : 447-452, 2005

8) Yamaura Y, Watanabe N, Ogasawara Y, Wada N, Kawamoto T, Toyota E, Akasaka T, Tanemoto K, Yoshida K : Geometric change of mitral valve leaflets and annulus after reconstructive surgery for ischemic mitral regurgitation: real-time 3-dimensional echocardiographic study. J Thorac Cardiovasc Surg 130 : 1459-1461, 2005

9) Watanabe N, Ogasawara Y, Yamaura Y, Yamamoto K, Wada N, Kawamoto T, Toyota 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 transthoracic real-time three-dimensional echocardiography. J Am Soc Echocardiogr 19 : 71-75, 2006

10) Tsukiji M, Watanabe N, Yamaura Y, *et al.* : Three-dimensional quantitation of mitral valve coaptation by a novel software system with transthoracic real-time three-dimensional echocardiography. J Am Soc Echocardiogr 21 : 43-46, 2008

11) Otsuji Y, Handschumacher MD, Liel-Cohen N, Tanabe H, Jiang L, Schwammenthal E, Guerrero JL, Nicholls LA, Vlahakes 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 37 : 641-648, 2001

12) Otsuji Y, Kumanohoso T, Yoshifuku S, Matsukida K, Koriyama C, Kisanuki A, Minagoe S, Levine RA, Tei C : Isolated annular dilation does not usually cause important functional mitral regurgitation: comparison between patients with lone atrial fibrillation and those with idiopathic or ischemic cardiomyopathy. J Am Coll Cardiol 39 : 1651-1656, 2002

13) Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ : Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: A quantitative clinical study. Circulation 102 : 1400-1406, 2000

14) Douglas PS, Reichek N, Hackney K, Ioli A, Sutton MG : Contribution of afterload, hypertrophy and geometry to left ventricular ejection fraction in aortic valve stenosis, pure aortic regurgitation and idiopathic dilated cardiomyopathy. Am J Cardiol 59 : 1398-1404, 1987