Mitral Valvular Coaptation-Zone Area Is Associated with the Severity of Atherosclerosis Assessed by Cardio-Ankle Vascular Index
Real-Time 3D Echocardiographic Analysis

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Summary
Preservation of the mitral valve (MV) size is essential for valve function, and a reduced MV coaptation-zone area increases the risk of developing functional mitral regurgitation (FMR). We aimed to determine if the MV leaflet and coaptation-zone areas were associated with the severity of atherosclerosis assessed by cardioankle vascular index (CAVI) in patients with normal left ventricle (LV) systolic function and size by real-time 3D echocardiography (RT3DE).

We performed RT3DE analysis in 66 patients with normal LV size and ejection fraction who underwent 2D echocardiography and CAVI. MV coaptation-zone areas were measured by custom 3D software and indexed by body surface area (BSA). The associations of clinical factors and mean CAVI with MV leaflet and coaptation-zone areas were evaluated by univariable and multivariable linear regression analyses.

On univariable analysis, MV leaflet area/BSA was significantly associated with age ($r = -0.335, P = 0.0069$) and mean CAVI ($r = -0.464, P < 0.001$), and MV coaptation-zone area was significantly associated with age ($r = -0.626, P < 0.001$), hypertension ($r = -0.626, P < 0.001$), dyslipidemia ($r = -0.626, P < 0.001$), E/e' ($r = -0.626, P < 0.001$), and CAVI ($r = -0.740, P < 0.001$). On multivariable analysis, mean CAVI was independently associated only with MV leaflet area/BSA (standardized coefficient = −0.611, $P < 0.001$) and MV coaptation-zone area/BSA (standardized coefficient = −0.74, $P < 0.001$).

In patients with normal LV systolic function and size, MV leaflet and coaptation-zone areas might be reduced according to advancing atherosclerosis. Patients with atherosclerosis might be at increased risk of developing FMR.

Key words: Mitral valve, Functional mitral regurgitation

Functional mitral regurgitation (FMR) is a common complication in patients with ischemic and dilated cardiomyopathy, which is associated with developing heart failure and poor clinical outcome. It is critical to understand the pathophysiology of FMR in order to establish strategies for its prevention and therapy. There is much experimental and clinical evidence that tethering of the mitral valve (MV) leaflet by a dilated LV and papillary muscle displacement is a key mechanism for the generation of FMR in addition to mitral annular dilation.

Recently, mitral leaflet size has been recognized as a possible underlying mechanism of progression of FMR, because the size of the MV leaflets is critical for preservation of the valve coaptation-zone and closure of the MV. The size of MV leaflets may be dynamically influenced by multiple factors. There are compensatory and intrinsic metabolic events occurring within the leaflets, named endothelial-mesenchymal transdifferentiation capacity. Furthermore, in patients with a dilated LV, mitral leaflets lengthened due to stress imposed by tethering may compensate for a reduced mitral coaptation-zone area. On the other hand, some patients might have FMR without significant LV dilation, as reported in those with aortic
stenosis, suggesting that atherosclerosis-related risk factors may hinder compensatory mitral leaflet elongation by affecting leaflet degeneration and size. In a previous study, we found that some atherosclerosis-related risk factors were associated with mitral leaflet size and coaptation. We hypothesized that the cardio-ankle vascular index (CAVI), which is widely used for assessing atherosclerosis comprehensively, may be associated with MV leaflet size. The aim of this study was to determine the association between the MV leaflet and coaptation-zone areas and the degree of atherosclerosis as assessed by CAVI or other clinical factors in patients with normal LV systolic function and size by real-time 3-dimensional echocardiography (RT3DE).

**Methods**

**Study subjects:** We acquired 3D echocardiographic volume data in consecutive subjects who underwent conventional echocardiography using a commercially available iE 33 echocardiography (Philips, Andover, MA, USA) for screening heart disease or assessing cardiac function. The subjects visited our hospital for medical care or suspicion of various diseases. Out of the pooled 3D data set, we screened subjects who underwent CAVI and had normal LV systolic function and size according to our 2D echocardiographic screening criteria, and added retrospective 3D echocardiographic analysis. Our 2D echocardiographic screening criteria were normal LV dimensions (an indexed LV end-diastolic diameter: males < 3.2 cm/m²; females < 3.3 cm/m²) and systolic function (LV ejection fraction ≥ 50%) without regional LV wall motion abnormalities. Consequently, the study enrolled 112 patients with normal LV dimensions and ejection fraction, and excluded patients with cardiomyopathy, atrial fibrillation, and significant valvular heart disease, except for FMR in which MV was structurally normal, as all of the above might influence mitral leaflet size. We also excluded patients with peripheral artery diseases (ABI < 0.9). Furthermore, based on a previous study that reported normal values of 3D echocardiographic measurements and their gender differences, we enrolled only cases who had normal LV size by 3D echocardiography (LV end-diastolic volume index of 26~74 mL/m² for males, and 28~64 mL/m² for females). We collected clinical data on each patient at the time of the first diagnosis and during the follow-up period from medical records. We also determined if patients had hypertension, diabetes, dyslipidemia, coronary artery disease (CAD), chronic kidney disease (CKD), ischemic stroke, heart failure, or a regular smoking habit, and if they were on hemodialysis. Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg measured repeatedly, or the use of antihypertensive therapy. Diabetes mellitus was defined as an overnight fasting serum glucose ≥ 126 mg/dL on at least two separate occasions, or treatment with antidiabetic therapy. Dyslipidemia was defined as a serum level of total cholesterol ≥ 220 mg/dL, triglycerides ≥ 150 mg/dL, low-density lipoprotein (LDL) cholesterol ≥ 140 mg/dL, and high-density lipoprotein (HDL) cholesterol < 40 mg/dL, or the use of lipid-lowering therapy. The presence of CAD was defined as a history of > 50% diameter stenosis in a major coronary artery based on coronary angiography or computed tomography. CKD was defined as a gradual loss of renal function over time that had progressed to 2nd stage CKD (eGFR 60-90 mL/minute/1.73 m²) or more severe stages. Ischemic stroke was diagnosed based on the findings of magnetic resonance imaging.

This cross-sectional study was approved by the institutional ethics committee of the University of Tokyo (#3825), and the requirement of informed consent was waived as we used de-identified data routinely collected during daily practice.

**Conventional echocardiography:** Two-dimensional (2D) and color Doppler imaging was performed to screen for valvular stenosis or regurgitation. LV mass and left atrial (LA) volume index were measured with 2D echocardiography, according to guidelines. We used the cube formula to calculate LV mass during the end-diastolic period: 

\[
LV\ mass = 0.8 \times (IVST + LVID + PWT)^2 - LVID^3 + 0.6 \times (IVST + interventricular septal wall thickness; LVID, LV internal diameter; PWT, posterior wall thickness.)
\]

LV mass index was calculated as LV mass/body surface area (BSA). LA volume was measured using the biplane disks method in the apical 2- and 4-chamber views. LA volume index was calculated as LA volume/BSA. We obtained transmitial diastolic flow by pulsed-wave Doppler from the apical 4-chamber view. Peak velocities of the early (E-wave) and late (A-wave) phases of the mitral inflow pattern from Doppler recordings were measured in the apical 4-chamber view, and their ratio (E/A) was calculated. The peak early diastolic (e') velocity of the septal mitral annulus was measured by pulsed tissue Doppler imaging in the apical 4-chamber view. The ratio of the E-wave to the e' velocity (E/e') was calculated as an index of LV filling pressure. The severity of MR was determined according to the current guidelines.

**3D echocardiographic data acquisition and LV volume measurement:** We used an iE33XMATRIX system (Philips, Andover, MA, USA) equipped with a highly ergonomic X5-1 transducer for RT3DE acquisition. Transthoracic 3D images were taken from the apical window during a breath-hold with the patient in the lateral decubitus position. Full-volume 3D volumetric data were obtained by combining 4 ECG-triggered, wedge-shaped sub-volumes. The recorded RT3DE data sets included the complete MV anatomic apparatus, and the entire LV in the pyramidal data set. Frame rates (16-22 frames/second) were selected based on imaging depth (12-16 cm). We used commercially available Q-lab 3D computer software (Philips, Andover, MA, USA) to determine the LV end-diastolic and end-systolic volumes (LVEDV and LVESV), and the LV volume was calculated using the multipleplane Simpson method. Ejection fraction (EF %) was calculated as: 

\[
EF\% = 100 \times \frac{LVEDV - LVESV}{LVEDV}
\]

**3D echocardiographic quantification of the mitral complex:** In the same manner as in our previous study, custom software (Realview, YD, Nara, Japan) was used to analyze the mitral complex geometry from the RT3DE volume data, according to previous studies. Initially, the time of MV closure onset was identified. The 3D
Figure 1. Mitral valvular parameters and papillary muscle apparatus at the time of MV closure onset (A) and mid-systole (B). A: The yellow points represent the mitral annulus in the sagittal plane. The green points represent the MV leaflets in the frontal plane. We marked the mitral annulus and traced the mitral leaflets in the same way on each of the 18 equally-segmented, rotated images. Then, 3D images of the mitral annulus and leaflets were automatically constructed by rotation of the MV annulus in the sagittal plane and MV leaflet in the frontal plane in each segmented image, and these images were used to quantify parameters of MV geometry at the onset of MV closure. B: The same images of the mitral apparatus at mid-systole. AL and PM indicate anterolateral and posteromedial papillary muscle, respectively.

A volumetric image was automatically cropped into 18 sequential planes spaced at equal radial distances (10°), and the anterior-posterior (A-P) and medial-lateral (M-L) planes of the MV annulus position were objectively determined by the aortic valvular and MV geometries among these planes. Next, the sagittal planes of the MV depicted in all 18 sequential plane images were traced. From the above, 3D images of the mitral annulus, leaflets were finally reconstructed automatically (Figure 1A). Additionally, the timing of mid-systole was determined, and the 3D reconstruction of the mitral apparatus was repeated in the same manner as above (Figure 1B).

From the reconstructed 3D images of the MV apparatus, MV parameters were calculated by Realview™ at the time of MV closure and mid-systole, as previously described.11) The MV leaflet area was determined as the tenting area at the time of MV closure and mid-systole, as previously described.11) The MV leaflet area was determined as the tenting area at the time of MV closure onset. MV coaptation-zone area was calculated by subtracting the MV tenting area at mid-systole from the MV tenting area at the MV closure onset (Figure 1A and B). MV leaflet and coaptation zone areas were indexed by BSA according to our previous study.11) For assessing the reproducibility of 3D echo quantification of mitral leaflet size and coaptation-zone areas, two independent observers performed 3D echocardiographic measurements, and one observer repeated the measurements subsequently in 10 cases.

Cardio-ankle vascular index: CAVI was measured by the VS2000 system (Fukuda Denshi, Tokyo) for assessing atherosclerosis18,19) at the discretion of the attending physician. The mean CAVI was calculated as the average of right and left CAVI.

Statistical analysis: All data are expressed as the mean ± SD for continuous variables and as percentages for categorical variables, and all statistical analyses were conducted utilizing SPSS24.0 software (SPSS Inc, Chicago, IL, USA). Pearson’s linear correlation analysis was used to determine the correlations between the MV parameters and the echocardiographic and clinical variables. Multivariable linear regression analysis was performed to assess the factors that determined the MV leaflet area and coaptation-zone area. Variables with $P < 0.10$ on univariable analysis were incorporated into the multivariable lin-
ear regression model. Statistical significance was defined as a two-tailed P-value < 0.05.

Results

Out of 112 enrolled cases, 46 were excluded from 3D echo analysis because of poor 3D echocardiographic images of MV, significant LV dilatation by 3D echocardiographic measurements, or peripheral artery disease. Consequently, we performed 3D echo analysis in 66 out of 112 cases (58.9%). Although we did not exclude patients with FMR, none of our study patients had significant MR (no MR in 7 cases (10.6%), trivial MR in 55 cases (83.3%), mild MR in 4 cases (6.1%)). Only one patient had a history of hospitalization due to heart failure, although the condition was stable when he underwent echocardiography (New York Heart Association functional class I and serum BNP = 60.1 pg/mL). Other patients had no history of heart failure. Table I shows the characteristics of the 66 patients and the results of 3D measurements of the LV, conventional echocardiographic parameters, and CAVI. The results of 3D measurements of MV parameters are summarized in Table II. The average MV leaflet area was 10.7 ± 1.4 cm², and the average MV coaptation-zone area was 1.3 ± 0.4 cm². Intraobserver and interobserver variability of MV leaflet area as assessed by the average measures of intra-class correlation coefficient were 0.976 (P < 0.001) and 0.839 (P = 0.007), and those for MV basal-clear zone area were 0.964 (P < 0.001) and 0.912 (P < 0.001), reflecting good reproducibility of the measurement.

The associations of MV leaflet area/BSA and MV coaptation-zone area/BSA with the clinical, echocardiographic parameters, and CAVI were examined by univariable and multivariable linear regression analyses (Tables III, IV). On univariable analysis, while MV leaflet area/BSA was significantly associated with age and mean CAVI, mean CAVI was the factor most closely associated with MV leaflet area/BSA (r = −0.464, P < 0.001, Figure 2A). On multivariable analysis, mean CAVI (standardized coefficient = −0.44, P = 0.015) was independently associated with MV leaflet area/BSA (Table III). On univariable analysis, MV coaptation-zone area/BSA was significantly associated with age, hypertension, dyslipidemia, echocardiographic LV diastolic parameter E/e’, and mean CAVI. Among them, mean CAVI was strongly associated with MV coaptation-zone area/BSA (r = −0.74, P < 0.001, Figure 2B). On multivariable analysis, mean CAVI was independently associated with MV coaptation-zone area/BSA (standardized coefficient = −0.611, P < 0.001) (Table IV). We found 5 cases (7.6%) with mild mitral annular calcification out of 66 cases. However, there was no significant relationship between mitral annular calcification and MV leaflet and coaptation zone areas, CAVI, or other clinical factors, probably because of the small number of these cases. Furthermore, the mitral annular circumference/BSA was significantly related to neither coaptation zone area/BSA (P = 0.618) nor mean CAVI (P = 0.518). For assessing the dynamic change of mitral annulus, we calculated the dynamic change of annular circumference as annular circumference/BSA in the onset of MV closure-annular circumference/BSA in the mid-systole. The dynamic change of annular circumference was also not significantly related to either coaptation zone area/BSA (P = 0.361) or mean CAVI (P = 0.399).

Table I. Patient Characteristics and the Results of Echocardiography and CAVI

| Characteristic                  | n = 66 |
|--------------------------------|--------|
| Age (years)                    | 66 ± 13|
| Male                           | 42 (63.6%) |
| Body surface area (m²)         | 1.7 ± 0.2 |
| Body mass index (kg/m²)        | 24.3 ± 4.4 |
| Heart rate (bpm)               | 69 ± 11 |
| Systolic blood pressure (mmHg) | 136 ± 23 |
| Diastolic blood pressure (mmHg)| 73 ± 14 |

Comorbidities

- Hypertension: 41 (62.1%)
- Type II diabetes mellitus: 26 (31.8%)
- Dyslipidemia: 33 (50.0%)
- Coronary artery disease: 21 (31.8%)
- Ischemic stroke: 6 (9.1%)
- Chronic kidney disease: 16 (24.2%)
- Hemodialysis: 2 (3.0%)
- Smoking: 16 (13.8%)

3D Echocardiography

- LVEDV index (mL/m²): 54.5 ± 6.1
- LVESV index (mL/m²): 20.3 ± 3.0
- LV ejection fraction (%): 62.8 ± 3.4
- Basal-clear zone area (cm²): 10.7 ± 0.4
- Leaflet area (cm²): 8.35 ± 0.8
- Annular circumference (mm): 104.7 ± 16.3
- Coaptation zone area (cm²): 9.4 ± 1.2

LVEDV indicates left ventricular end-diastolic and end-systolic volumes; LVESV, left ventricular end-systolic volumes; LV, left ventricular; LA, left atrial; and CAVI, cardio-ankle vascular index.

Table II. Mitral Valve Geometrical Parameters at the Onset of MV Closure and Mid-Systole

| MV variables         | At MV closure onset Mean ± SD | Range   | At cardiac mid-systole Mean ± SD | Range   |
|----------------------|-------------------------------|---------|---------------------------------|---------|
| Annular area (cm²)   | 8.6 ± 1.0                     | 6.7—11.5| 7.7 ± 1.0                       | 5.6—10.3|
| Annular circumference (mm) | 104.7 ± 16.3          | 92.0—211.1| 99.4 ± 6.3                      | 84.6—114.5|
| Leaflet area (cm²)   | 10.7 ± 1.4                    | 8.35—15.1| —                               | —       |
| Coaptation zone area (cm²) | —                           | —       | 9.4 ± 1.2                       | 7.0—12.6|

MV indicates mitral valve.
Relationship between MV leaflet and atherosclerosis: As previous studies have suggested,2,3,6-9) MV leaflet and coaptation-zone area/BSA (cm²/m²) were independently negatively associated with mean CAVI. Atherosclerosis-related risk factors associated with increased CAVI may affect the MV size and closure function. In particular, the reductions of both MV leaflet and coaptation-zone area/BSA were independently negatively associated with mean CAVI. Atherosclerosis-related risk factors associated with increased CAVI may affect the MV size and closure function.

| Risk Factor                     | Univariate analysis | Multivariable analysis |
|--------------------------------|---------------------|-----------------------|
|                                | Correlation coefficient | P value | Standardized coefficient | P value |
| Age (years)                    | -0.335              | 0.006                | 0.010                    | 0.955               |
| Heart rate (bpm)               | 0.058               | 0.646                |                          |                    |
| Systolic BP (mmHg)             | -0.171              | 0.169                |                          |                    |
| Diastolic BP (mmHg)            | -0.067              | 0.592                |                          |                    |
| Hypertension                   | -0.069              | 0.583                |                          |                    |
| Type II diabetes mellitus      | -0.127              | 0.309                |                          |                    |
| Dyslipidemia                   | -0.189              | 0.129                |                          |                    |
| Coronary artery disease        | 0.052               | 0.676                |                          |                    |
| Ischemic stroke                | 0.096               | 0.442                |                          |                    |
| Chronic kidney disease         | 0.134               | 0.282                |                          |                    |
| Hemodialysis                   | 0.002               | 0.987                |                          |                    |
| Smoking                        | 0.132               | 0.291                |                          |                    |
| LVEDV index (mL/m²)            | -0.026              | 0.837                |                          |                    |
| LVESV index (mL/m²)            | 0.13                | 0.296                |                          |                    |
| LV ejection fraction (%)       | -0.237              | 0.055                | -0.143                   | 0.217               |
| LV mass index (g/m²)           | -0.037              | 0.768                |                          |                    |
| LA volume index (mL/m²)        | 0.022               | 0.861                |                          |                    |
| E/e'                           | -0.107              | 0.391                |                          |                    |
| Mean CAVI                      | -0.464              | < 0.001              | -0.440                   | 0.015               |

BSA indicates body surface area; BP, blood pressure; LV, left ventricle; LVEDV and LVESV, left ventricular end-diastolic and end-systolic volumes; LA, left atrial; MV, mitral valve; and CAVI, cardio-ankle vascular index.

Discussion
In this study, we explored the clinical factors associated with MV leaflet and coaptation-zone areas indexed volume. We found that MV leaflet area/BSA and MV coaptation-zone area/BSA might be affected by some clinical factors even in patients with normal LV size and systolic function. In particular, the reductions of both MV leaflet and coaptation-zone area/BSA were independently negatively associated with mean CAVI. Atherosclerosis-related risk factors associated with increased CAVI may affect the MV size and closure function.
CAVI ASSOCIATED WITH MV LEAFLETS BY 3D ECHO

Figure 2. Correlations of mitral valvular leaflet area/BSA (A) and coaptation-zone area/BSA (B) with mean CAVI. Both MV leaflet and coaptation-zone areas were significantly associated with mean CAVI. CAVI indicates cardio-ankle vascular index.

coaptation-zone areas, which are essential components of MV closure function, are significantly influenced by tethering and the subvalvular apparatus. Although a close relationship between MV leaflet and coaptation-zone areas was observed,10 MV coaptation-zone area might be more susceptible to many clinical factors and more diverse, as shown in the present study, presumably related to the variable severity of FMR regardless of LV size. In a previous study,11 we found that MV leaflet area might be intrinsically determined by body size rather than age and LV size, and the MV leaflet area/BSA is relatively constant. On the other hand, some clinical factors also influenced MV leaflet and coaptation-zone area, but there was no strong determinant of these areas other than BSA.13

CAVI is widely used for assessing atherosclerosis as a blood pressure-independent parameter of arterial stiffness at measuring time and reported to be associated with cardiovascular disease risks and events.18,19 It is known that CAVI increases with age due to age-related atherosclerosis, but it further increases by reflecting multiple atherosclerosis-related factors, such as smoking, obesity, hypertension, dyslipidemia, and abnormal glucose metabolism.18,19 Our results suggest that MV leaflet and coaptation-zone areas can be reduced with advancing atherosclerosis by multiple clinical factors assessed by CAVI, rather than any single factor. We speculate that atherosclerosis, which is represented by mean CAVI, might be associated with degenerative changes in MV leaflet tissue, which hinders compensatory mitral leaflet elongation. Our finding is consistent with previous studies that patients with aortic stenosis often suffer from FMR without significant LV dilatation,15,16 because in the current era most aortic stenosis develops as a consequence of risk factors and pathological processes similar to those of atherosclerosis. Furthermore, patients with ischemic cardiomyopathy may be complicated with FMR with relatively smaller LV than those with dilated cardiomyopathy.41 MV leaflet and coaptation-zone areas are presumably reduced in association with ischemic heart disease. Not only geometric differences of papillary muscles between two entities, but degenerative change of MV in ischemic cardiomyopathy might be associated with this phenomenon.

Degenerative change of MV and atherosclerosis: On histology, the cross-sectional structure of MV leaflets is divided into 3 layers (atrialis, spongiosa, fibrosa). In the atrialis layer, there are endothelia, subendothelial connective tissue, and elastin sheets, which have the same histological structure as in vascular layers, for maintaining the elasticity of the leaflets.27 Pathological studies28 have indicated that foam cells appear in early atherosclerotic lesions,29 and can also be found in affected patients on the endothelium of mitral leaflets. Consequently, in patients with advanced atherosclerosis, the atrialis layer of MV leaflets might be degenerated, presenting with a reduction of the MV leaflet area and coaptation ability, which might be one of the mechanisms for the pathology of FMR.

Clinical implications: In this study, we have demonstrated that the MV leaflet and coaptation-zone areas, which are essential for valve function, may be affected by atherosclerotic factors. Our findings suggested that patients with atherosclerosis might be at a higher risk of developing FMR, even if LV enlargement is mild. When considering a treatment or preventive strategy for FMR, it is necessary to evaluate the change of leaflet and coaptation-zone areas associated with atherosclerosis. Intensive treatment for arteriosclerosis might reduce the risk of developing FMR in patients with dilated or ischemic cardiomyopathy.

Limitations: Since this retrospective study was conducted at a single-center and we enrolled only subjects who had both echocardiography and CAVI, there may have been selection bias in our study population. A larger prospective study is needed to confirm our results. The mitral leaflet area was calculated at the onset of mitral leaflet closure. However, it has been shown that the mitral leaflet stretches during systole.30 Accordingly, the mitral leaflet area measurements and the coaptation-zone area may have been underestimated. Although MV geometry was evaluated by 3D echocardiography in this study, it still has limited spatial and temporal resolutions. Further advancement of 3D echocardiography or other imaging modalities may bring greater and more precise insight into this research area. The study subjects did not include patients with significant FMR. Therefore, further study is needed to examine the relationship between the MV leaflet area and the mechanisms of FMR. Finally, we did not analyze the association between medications and MV area. In particular,
renin-angiotensin system inhibitors may potentially affect mitral leaflet metabolism. Further study that explores the relationship between MV leaflet area and therapeutic drugs would be of interest.

Conclusions

In patients with normal LV systolic function and size, MV leaflet and coaptation-zone area might be reduced according to advancing atherosclerosis. Patients with atherosclerosis might be at increased risk of developing FMR due to loss of compensatory elongation of MV.

Disclosure

Conflicts of interest: The authors declare that they have no relationships with any industry.

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