The Adaptive Remodeling of the Anterior Mitral Leaflet and Chordae Tendineae Is Associated with Mitral Valve Function in Advanced Ischemic and Nonischemic Dilated Cardiomyopathy

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Summary

The degree or nature of functional mitral regurgitation (MR) is not necessarily correlated with the size or function of the left ventricle (LV). We hypothesized that the anatomical structure of the mitral valve (MV) complex might play a role in functional MR in ischemic or nonischemic dilated cardiomyopathy (DCM).

The structure of the LV and MV complex in DCM patients (n = 29) was assessed using electrocardiogram-gated 320-slice computed tomography and was compared with that in healthy patients (n = 12). Twenty-five DCM patients with mild or low MR (DCM-lowMR) had markedly greater length, diameter, and sphericity index of the LV and a larger tenting area than the controls. The distance between the papillary muscle (PM) tip and the mitral annular plane was not different between DCM-lowMR and normal hearts despite the greater LV length observed in DCM-lowMR. Furthermore, DCM-lowMR had markedly longer chordae tendineae (DCM-lowMR: 24 [20-26] mm; controls: 14 [13-16] mm; \( P < 0.01 \)) and larger anterior leaflets (DCM-lowMR: 30 [27-31] mm; controls: 22 [20-24] mm; \( P < 0.01 \)), thus suggesting the adaptive remodeling of the MV complex.

Four DCM patients with moderate-severe MR had unbalanced remodeling, such as excessive LV dilatation, short anterior mitral leaflets, and short chordae tendineae.

The development of functional MR might be associated with the remodeling of LV and MV components, such as the PMs, chordae tendineae, or anterior MV leaflets. Detailed anatomical assessments of the LV and MV complex would contribute to the adequate staging of ischemic or nonischemic DCM.

Key words: Functional mitral regurgitation, Computed tomography, Remodeling of mitral valve leaflet

Clinical Study

Functional mitral regurgitation (MR) is associated with poor outcomes in patients with ischemic and nonischemic dilated cardiomyopathy (DCM).\(^1\)\(^-\)\(^4\) Given that functional MR is caused by a dilated left ventricle (LV) enlarging the annulus of the mitral valve (MV), which then tethers the MV leaflets to the LV, functional MR is considered an indicator of DCM progress.\(^5\)\(^-\)\(^7\) Functional MR is also a therapeutic target for enhancing the reverse remodeling of the LV in advanced DCM in certain populations, although the indications or procedures for functional MR associated with DCM are not yet fully established.\(^8\)\(^-\)\(^11\) The degree or nature of functional MR is not necessarily correlated with the size of the LV or the degree of MV tethering, thus suggesting that the structure of the LV and the MV, which differs in individual patients with DCM, may be the key to determining the function of the MV in advanced DCM.\(^5\)\(^-\)\(^7\),\(^12\)-\(^14\)

Recently, electrocardiogram (ECG)-gated cardiac computed tomography scanning was developed to study the detailed structures of the heart, including the LV and MV.\(^10\)\(^-\)\(^11\) On the basis of the abovementioned information, we hypothesized that the anatomical structure of the LV and MV complex is a determining factor in the occurrence of functional MR in ischemic and nonischemic DCM. To test this hypothesis, we aimed to quantitatively analyze each component of the MV complex and the LV geometry in ischemic and nonischemic DCM patients by using 320-slice multidetector computed tomography (MDCT) and to assess the echocardiographic degree and nature of functional MR.

Methods

Study cohort: After gaining institutional review board approval, we collected the data required to perform this retrospective study. Forty-four patients who were clinically...
diagnosed with advanced ischemic and nonischemic DCM underwent 320-slice ECG-gated cardiac MDCT for anatomical and functional diagnostic purposes at Osaka University Hospital between January 2014 and April 2016. Eight patients who suffered from arrhythmia during the study and seven patients whose images were not appropriate for analysis were excluded from the study. The final cohort consisted of 29 DCM patients with ischemic (n = 18) and nonischemic (n = 11) etiologies with or without functional MR. Echocardiographically, the 16 patients with ischemic DCM and the 9 patients with nonischemic DCM exhibited mild or low MR, whereas 2 patients with ischemic DCM and 2 patients with nonischemic DCM exhibited moderate or severe MR. Twelve patients with normal cardiac function without MR who underwent ECG-gated cardiac MDCT for diagnostic purposes owing to possible coronary artery disease were included as controls (Table I). Although 6 of the 12 control patients showed stenosis in their coronary arteries, they could be enrolled as controls because they had normal LV function and wall thickness.

**Transthoracic echocardiography:** Standard 2D transthoracic echocardiography was performed in all patients by using a Philips IE33 echocardiography system (Philips Medical Systems, Andover, MA, USA) for diagnostic purposes within seven days of MDCT. The severity of MR was categorized according to the Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance: mild (regurgitant orifice area < 0.20 cm², regurgitant volume < 30 mL/beat, regurgitant fraction < 30%, and Doppler vena contracta width < 0.3 cm), moderate (regurgitant orifice area 0.20-0.39 cm², regurgitant volume 30-59 mL/beat, regurgitant fraction 30%-49%, and Doppler vena contracta width 0.3-0.6), or severe (regurgitant orifice area ≥ 0.40 cm², regurgitant volume ≥ 60 mL/beat, regurgitant fraction ≥ 50%, and Doppler vena contracta width ≥ 0.7 cm). The data in the official echocardiography report were included in the analysis.

**MDCT study-based data acquisition, reconstruction, and analysis:** All patients were examined under sinus rhythm by using 320-slice MDCT (Aquilion, Toshiba Medical Systems, Tokyo, Japan) according to the following protocol: 120 kV, 200-250 mA with automatic exposure control, 275 ms rotation time, and 320 mm × 0.5 mm collimation. Nonionic contrast medium (50 mL) (Iomeron 350, Bracco, Altana Pharma, Konstanz, Germany) were intravenously injected into the antecubital vein at a rate of 3-4.5 mL/second. Automated peak enhancement detection in the descending aorta was used to time the administration of the contrast bolus. Data acquisition was started automatically after the threshold level of 100 Hounsfield units was achieved and was performed during an inspiratory breath hold of 8-10 seconds. The ECG was recorded simultaneously to allow the retrospective gating and reconstruction of the data at the desired phases of the cardiac cycle. In patients with heart rates > 70 beats/minute, 12.5 mg of lantidol hydrochloride (Corebeta, Ono Pharmaceutical, Osaka, Japan) was intravenously injected to reduce the heart rate to < 70 beats/minute. Otherwise, three cardiac beats were acquired, thus resulting in a segment reconstruction algorithm with slightly lower temporal reconstruction. All images were transferred to a dedicated workstation for data analysis (AZE Virtual Place, AZE, Tokyo, Japan). The reconstruction thickness was 0.5 mm. A 10-image series of the cardiac cycle (0% of the R-R interval as early systole, 90% of the R-R interval as late diastole, reconstructed in 10%
The anatomy of the papillary muscles (PMs) was categorized by the number of heads and the type of insertion into the LV wall. The distance between the tips of the anterior/posterior PMs and the annular plane of the MV in the LV sagittal or coronal plane views was measured (Figure 1A). Furthermore, the length of the chordae tendineae was measured as the distance between the central point of A2-P2 coaptation and the tip of the posterior PM in the systolic phase (Figure 1C). Moreover, the intercommisural (CC) diameter, anteroposterior (AP) diameter, mitral annular perimeter, and the distance between fibrous trigones were measured in the MV short-axis view (Figure 1D). Furthermore, the coaptation index was calculated as the ratio of the distance between the root of the anterior mitral leaflet and the coaptation point on the mitral annulus to the mitral AP diameter. The longer arrow (y) represents the AP diameter of the MV. The ratio of x to y is the coaptation index. Ao, aorta; AP diameter, anteroposterior diameter; CC diameter, intercommisural diameter; LA, left atrium; LV, left ventricle; MV, mitral valve; and PM, papillary muscle.

**Figure 1.** Assessment of the LV and MV complex geometry. A: The long arrow between the apex and mitral annular plane represents the LV length in the LV coronal plane view. The short arrow represents the distance between the tip of the PM and the mitral annular plane. B: The arrow represents the LV diameter in the LV short-axis view. The ratio of the LV diameter to the LV length is denoted as the LV sphericity index. C: The chordae tendineae, which was considered the distance between the tip of the posterior PM and the central point of A2-P2 coaptation. D: The CC diameter, AP diameter, mitral annular perimeter, and distance between the fibrous trigones were measured in the MV short-axis view. E-F: Leaflet angles (α, β), leaflet lengths, tenting height, tenting area, and coaptation length measured in the MV sagittal view at the A2-P2 segment. The shorter arrow (x) represents the distance between the root of the anterior mitral leaflet and the coaptation point on the mitral annulus. The longer arrow (y) represents the AP diameter of the LV. The ratio of x to y is the coaptation index. Ao, aorta; AP diameter, anteroposterior diameter; CC diameter, intercommisural diameter; LA, left atrium; LV, left ventricle; MV, mitral valve; and PM, papillary muscle.

increments from 0% to 90%) was obtained. In all 10 phases, the phases with minimum and maximum LV volumes were selected as the systolic and diastolic images, respectively.

**MDCT data-based anatomical parameter measurements of the LV and MV:** The anatomical parameters of the LV and MV were measured using the data acquired in the 320-slice MDCT study. The end-diastolic and end-systolic volumes of the LV were measured from the trace of the LV wall muscle. The LV volumes were corrected for body surface area. The ejection fraction (EF) of the LV was calculated by dividing the end-systolic volume by the end-diastolic volume of the LV. Furthermore, we measured and calculated the following: 1) the longitudinal length of the LV, which was defined as the distance between the LV apex and the mitral annular plane in the LV sagittal or coronal plane view (Figure 1A); 2) the diameter of the LV, which was defined as the distance between the inside of the anterior wall and the posterior wall in the LV short-axis view (Figure 1B); and 3) the sphericity index of the LV, which was calculated by dividing the LV diameter by the LV length.

The anatomy of the papillary muscles (PMs) was categorized by the number of heads and the type of insertion into the LV wall. The distance between the tips of the anterior/posterior PMs and the annular plane of the MV in the LV sagittal or coronal plane views was measured (Figure 1A). Furthermore, the length of the chordae tendineae was measured as the distance between the central point of A2-P2 coaptation and the tip of the posterior PM in the systolic phase (Figure 1C). Moreover, the intercommisural (CC) diameter, anteroposterior (AP) diameter, mitral annular perimeter, and the distance between fibrous trigones were measured in the MV short-axis view (Figure 1D). Furthermore, the coaptation index was calculated as the ratio of the distance between the root of the anterior MV leaflet and the coaptation point on the annular plane (x) to the mitral AP diameter (y) in the MV sagittal view (Figure 1E):

\[
\text{coaptation index} = \frac{x}{y}
\]

Furthermore, the tenting area, the angles between the mitral annular plane and anterior or posterior leaflet in the systolic phase (α and β, respectively), the anterior and posterior leaflet lengths, and the coaptation length were measured in the same view (Figure 1E and F).

**Statistical analysis:** Data are presented as frequencies with percentages for categorical variables and as medians with interquartile ranges for continuous variables. Cate-
statistical analyses were performed using commercial software (JMP®13, SAS Institute Inc., Cary, NC). Statistical significance was defined as a $P$ value < 0.05.

**Results**

Globally enlarged and spherized LV in ischemic and nonischemic DCM with mild or low MR: The size, geometry, and function of the LV were compared between the controls and the DCM patients with mild or low MR. The controls had similar wall motion of the LV without regional irregularities, whereas the DCM patients with mild or low MR (either ischemic or nonischemic) had globally hypokinetic wall motion of the substantially enlarged LV with some regional irregularities, predominantly in ischemic DCM (Table I). The DCM patients with mild or low MR displayed significantly larger end-diastolic and end-systolic volumes and lower EF of the LV compared with the controls (Table II). Furthermore, the length and diameter of the LV were significantly larger in DCM patients with mild or low MR than those in the controls, whereas the sphericity index of the LV was significantly greater in the DCM patients with mild or low MR than that in the controls. There was no statistically significant difference in LV size and geometry between ischemic and nonischemic DCM patients with mild or low MR.

Anatomical and functional variation of the PMs in ischemic and nonischemic DCM with mild or low MR: On the basis of our MDCT-based anatomical study, the anatomy of the PMs was categorized by 1) the number of heads (ranging from I-III) and 2) the type of insertion into the LV wall (types A to C) on the basis of the classification of the morphologic variants of the PMs (Figure 2 A).13,19) The result shows that the majority of people (80%) among the DCM patients with mild or low MR had one or two heads of the anterior PM, but the number of heads of the posterior PM was more variable (42% had one or two heads, and 58% had three heads). By contrast, the DCM patients with mild or low MR had fewer heads in both anterior and posterior PMs than the controls. In particular, 75% of the DCM patients with mild or low MR had one or two heads in the posterior PMs. The distance between the tip of the PM and the mitral annular plane in the DCM patients with mild or low MR was not different from that in the control patients despite the greater length of the LV in the DCM patients with mild or low MR (Figure 2C).

Remodeling of the MV structure in DCM patients with mild or low MR: The structure of the MV, including the subvalvar apparatus, was quantitatively analyzed on the basis of MDCT data. As a result, the length of the chordae tendineae was significantly greater in the DCM patients with mild or low MR (24 [20-26] mm) than that in the controls (14 [13-16] mm, $P < 0.01$). Furthermore, the DCM patients with mild or low MR displayed a significantly larger CC diameter and AP diameter than the controls (Table III). The mitral annular perimeter in the DCM patients with mild or low MR was longer than that in the controls, whereas the distance between the fibrous trigones in the DCM patients with mild or low MR was not significantly different from that in the controls. Therefore, the posterior mitral annulus was predominantly dilated in the DCM with mild or low MR.

In the MV sagittal view, the DCM patients with mild or low MR showed a larger tenting area and larger angles between the annular plane and anterior/posterior leaflets in the systolic phase than the controls, thus suggesting that the mitral leaflets were tethered in the DCM patients with mild or low MR. The coaptation lengths in the DCM patients with mild or low MR (3.3 [2.8-3.8] mm) were significantly shorter than those in the controls (4.9 [3.9-5.6] mm, $P < 0.01$). Furthermore, patients in the DCM with mild or low MR group (30 [27-31] mm) had longer anterior mitral leaflets than the controls (22 [20-24] mm, $P < 0.01$), although the length of the posterior mitral leaflet was similar between the two groups (control: 16 [15-17] mm; DCM with mild or low MR: 16 [12-18] mm; $P = 0.62$). The coaptation index of the DCM patients with mild or low MR (0.79 [0.69-0.86]) was significantly higher than that of the controls (0.59 [0.55-0.67], $P < 0.01$), thus indicating that the coaptation site of the mitral leaflets moved in the posterior direction in the DCM patients with mild or low MR because of their longer mitral anterior leaflets.

Insufficient MV remodeling in DCM patients with moderate or severe MR: Among the DCM patients, four had moderate-severe functional MR echocardiographically. The geometry and anatomy of the LV and MV complex in the DCM patients with moderate or severe MR ($n = 4$) were compared with those in the DCM patients with mild or low functional MR ($n = 25$) to explore the potential mechanisms of functional MR (Figure 3). Three patients in the DCM with moderate or severe MR group (cases 1,
**Figure 2.** A: The anatomic variation of the PMs was classified according to the number of heads and insertions, as previously described.13,19. B: Anatomic variations of the PMs in control patients (n = 12) and DCM patients with mild or low MR (n = 25) are shown. The upper graphs represent variations in anterior PMs, and the lower graphs represent variations in posterior PMs. C: Graph showing the distance between the tip of the PMs and the mitral annular plane in the control and the DCM patients with mild or low MR in the systolic and diastolic phases. No statistically significant differences between the two groups were observed. DCM, dilated cardiomyopathy; PM, papillary muscle.

**Table III.** MV Geometry in the Control Patients and the DCM Patients with Mild or Low MR

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 12)</th>
<th>DCM with mild or low MR (n = 25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordae tendineae (mm)</td>
<td>14 (13-16)</td>
<td>24 (20-26)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CC diameter (mm)</td>
<td>36 (34-38)</td>
<td>41 (38-43)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>AP diameter (mm)</td>
<td>23 (22-24)</td>
<td>28 (27-30)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mitral annular perimeter (mm)</td>
<td>123 (115-128)</td>
<td>138 (133-148)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Distance between fibrous trigones (mm)</td>
<td>23 (21-26)</td>
<td>27 (26-30)</td>
<td>0.10</td>
</tr>
<tr>
<td>Tenting height (mm)</td>
<td>4 (3-5)</td>
<td>7 (6-9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Tenting area (mm²)</td>
<td>81 (69-116)</td>
<td>159 (138-199)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Anterior leaflet angle (α) (degree)</td>
<td>14 (10-25)</td>
<td>29 (24-38)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Posterior leaflet angle (β) (degree)</td>
<td>24 (14-32)</td>
<td>45 (35-56)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Coaptation length (mm)</td>
<td>4.9 (3.9-5.6)</td>
<td>3.3 (2.8-3.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Anterior leaflet length (mm)</td>
<td>22 (20-24)</td>
<td>30 (27-31)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Posterior leaflet length (mm)</td>
<td>16 (15-17)</td>
<td>16 (12-18)</td>
<td>0.70</td>
</tr>
<tr>
<td>Coaptation index</td>
<td>0.59 (0.55-0.67)</td>
<td>0.79 (0.69-0.86)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are median with IQR. AP diameter indicates anteroposterior diameter; CC diameter, intercommissural diameter; DCM, dilated cardiomyopathy; and MR, mitral regurgitation.
2, and 3) exhibited a longer mitral annular perimeter, higher LV end-systolic volume index, and larger tenting area than the third quartile in the DCM with mild or low MR group, thus suggesting that the tethering of the mitral leaflets and mitral annular dilatation were greater in the DCM patients with moderate or severe MR than in the DCM patients with mild or low MR (Table IV). The lengths of the chordae tendineae did not exceed the median in the DCM with mild or low MR, thus indicating that the remodeling of the chordae tendineae was insufficient to prevent the development of functional MR. However, the other patient in the DCM group with moderate or severe MR (case 4) displayed 141 mm of mitral annular perimeter, 78 mL/m² of LV end-systolic volume index, and 186 mm² of tenting area between the median and third quartile in the DCM with mild or low MR group. On the contrary, the anterior mitral leaflet and chordae tendineae in case 4 were shorter than the first quartile in the DCM with mild or low MR group, thus indicating that the remodeling of the anterior leaflet and chordae tendineae was insufficient to prevent the development of functional MR in this case.

### Discussion

The findings of this study suggest that DCM hearts with mild or low MR have a markedly greater length, diameter, and sphericity index of the LV than functionally normal hearts regardless of whether the etiology of DCM is ischemic or nonischemic. Patients with DCM of either etiology with mild or low MR showed a small number of PM heads. The distance between the PM tip and the mitral annular plane was not different between the DCM hearts with mild or low MR and normal hearts despite the greater length of the LV in the DCM heart with mild or low MR. Furthermore, the DCM hearts with mild or low MR had markedly longer chordae tendineae, longer MV annular perimeter, and larger anterior leaflets but not posterior leaflets, thus indicating that a smaller coaptation of the leaflets with tethering occurred. By contrast, DCM hearts with moderate-severe MR displayed a different structure of the MV complex from those with mild or low MR, such as excessively large LVs, short chordae tendineae, or short anterior MV leaflets.

The structure of the LV and MV complex was quantitatively analyzed using an ECG-gated 320-slice MDCT in normal and DCM hearts. MDCT revealed the minute structures of the components, such as the PMs, which have a larger number of heads and insertions into the posterior PM than the anterior PM in normal hearts, as reported in previous postmortem studies. DCM hearts with mild or low MR had a smaller number of heads and insertions of the PMs than normal hearts regardless of the DCM etiology, thus possibly indicating that PMs might degenerate and atrophy according to the progression of LV remodeling. By contrast, the distance between the tip of the PM and the mitral annular plane in DCM hearts with mild or low MR was not different from that in normal hearts, thus possibly suggesting that the PMs underwent adaptive remodeling to inhibit the occurrence of functional MR.

The adaptive remodeling of the LV/MV components in the DCM heart with mild or low MR would include the passive and/or active elongation of the chordae tendineae and the anterior mitral leaflet, as shown in the MDCT results in this study. Deja, et al. reported that the length of the chordae tendineae is associated with the degree of functional MR, this result supports the findings of the present study. Moreover, in an animal model of ischemic DCM, it has been repeatedly reported that the mechanical stretching created by the tethering of the MV leaflets causes the elongation of the MV leaflets via epithelial-mesenchymal transition, cellular proliferation, and matrix remodeling; these results further support the findings of the present study.

This study provided a novel finding that the leaflet of the MV is elongated in the anterior leaflet but not in the posterior leaflet in DCM hearts with mild or low MR. This finding may be supported by the theory that the mechanical stretching produced by the posteriorly located PMs in the DCM heart is more potent in the anterior MV leaflet than in the posterior leaflet. In other words, the anterior and posterior MV leaflets are respectively stretched longitudinally and vertically, thus leading to the predomi-
Figure 3. Representative images of the LV and MV complex anatomy in the controls and DCM patients with mild or low MR; images of all DCM patients with moderate or severe MR. The MV short-axis view is shown in the left panels, the MV sagittal view is shown in the middle panels, and the LV sagittal view is shown in the right panels. In the DCM with moderate or severe MR group, three patients (DCM with moderate or severe MR cases 1, 2, and 3) exhibited longer mitral annular perimeters and larger LV volumes and tenting areas than patients in the DCM with mild or low MR group. The other patients (DCM with moderate or severe MR case 4) had comparable LV volumes and tenting areas to the DCM with mild or low MR patients, although the anterior mitral leaflet and chordae tendineae in this case were shorter than those in the DCM with mild or low MR patients and were similar to those in the control patients. LV, left ventricle; MV, mitral valve; PM, papillary muscle; DCM, dilated cardiomyopathy; and MR, mitral regurgitation.
nant elongation of the anterior MV leaflet and the movement of the coaptation point toward the posterior leaflet in the DCM heart. This theory might be supported by the findings in DCM hearts with moderate-severe MR in this study. Case 4 in the DCM with moderate or severe MR group had relatively or definitely shorter sizes of anterior MV leaflets than those of the DCM hearts with mild or low MR, although the mechanisms underlying the insufficient remodeling of the anterior leaflet remain unclear. Furthermore, there should be criteria representing the sufficient remodeling of each component to apply this concept to clinical settings.

Hetzer, et al.\textsuperscript{27} reported that the extension of the posterior MV annulus and the distance between the annulus and PMs would result from LV dilatation, thus accelerating the development of functional MR by tethering the leaflets and making the coaptation of the leaflets more shallow in the DCM heart.

The results of this study suggest that the development of functional MR may be associated with the remodeling of each component of the LV and MV, such as the PMs, chordae tendineae, or anterior MV leaflets. Furthermore, the findings of this study substantially contribute to contemporary surgical and conservative treatments. First, this study performed the minute assessment of the structure of the LV and MV by using MDCT. Second, the minute assessment of LV/MV structures is useful in estimating the stage of LV remodeling in the DCM heart. Moderate functional MR with large enough anterior MV leaflets would suggest advanced LV remodeling, for which cardiac transplantation or mechanical assistance device implantation may be indicated. By contrast, moderate functional MR with small MV leaflets may be a target for MV surgery, which might lead to the reverse remodeling of the LV. Finally, the indication and/or procedures of MV surgery for functional MR in DCM are somewhat clarified by the findings of this study. An MR that is predominately caused by a definitely short length of the anterior MV leaflet should be repaired using full-ring annuloplasty, which enlarges the coaptation. These findings may be critically important in determining the indications and procedures for transcatheter MV intervention in advanced DCM.

This study was limited by factors associated with the study of rare diseases. The cohort had heterogeneous backgrounds, etiologies, and/or cardiac function. The study cohort included both ischemic and nonischemic etiologies, but the stages of the disease were consistently advanced in all patients. As a result, cardiac structure or function was not significantly different between the ischemic and nonischemic DCM patients. Furthermore, the number of patients was small for this type of anatomical and functional study. However, no type-II statistical errors occurred in the controls and the DCM patients with mild or low MR. These errors occur when the number of patients is too small to detect an effect. Therefore, the number of patients included in this study was sufficient. Further structural and/or functional analyses, such as segmental analysis of the MV, would only be possible in a study that included a larger number of patients. The number of DCM patients with moderate or severe MR was insufficient to analyze the statistical significance of the results. Although all of the DCM patients with moderate or severe MR had structures that are different from the DCM patients with mild or low MR, a large number of DCM patients with moderate or severe MR was needed to clarify the mechanisms of occurrence or development of functional MR.

In conclusion, DCM hearts with mild or low MR exhibited adaptive remodeling of each LV and MV component, such as the PMs, chordae tendineae, or anterior MV leaflets; this type of remodeling might suppress the development of functional MR. DCM hearts with moderate or severe MR showed unbalanced remodeling, such as short MV leaflets, short chordae tendineae, and excessively large LVs. These detailed anatomical assessments of the LV and MV complex may contribute to the adequate staging of ischemic or nonischemic DCM.

**Acknowledgment**

I would like to express my heartfelt appreciation to Yasuhiro Yanagawa, whose support and insightful comments were invaluable during the course of this study.

**Disclosures**

**Conflicts of interest:** The authors declare no conflicts of interest associated with this manuscript.

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