The importance of papillary muscle dyssynchrony in predicting the severity of functional mitral regurgitation in patients with non-ischaemic dilated cardiomyopathy: a two-dimensional speckle-tracking echocardiography study

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Aims
In our study, we investigated the impact of papillary muscle systolic dyssynchrony (DYS-PAP) and the configuration of mitral leaflets in the prediction of significant functional mitral regurgitation (MR) with two-dimensional (2D) speckle-tracking strain analysis in non-ischaemic dilated cardiomyopathy (DCM) patients with sinus rhythm.

Methods
Thirty-six non-ischaemic DCM patients (left ventricular ejection fraction ≤40%) with sinus rhythm were recruited. The quantification of functional MR was performed using the proximal isovelocity surface area method. The configuration of mitral leaflets [mitral annulus, coaptation height (CH), and tethering distances for papillary muscles] was evaluated in the parasternal long-axis and apical four-chamber views. The assessment of DYS-PAP was performed by applying 2D speckle-tracking imaging to the apical four-chamber view for anterolateral papillary muscle and to the apical long-axis view for posteromedial papillary muscle.

Results
Fifteen (41.6%) patients had mild MR and 21 (58.3%) patients had moderate or moderate-to-severe MR. Patients with higher levels of MR had larger mitral annulus size (P = 0.02), tethering-AL (P = 0.04), higher MR volume (P < 0.0001), effective regurgitant orifice area (P < 0.0001), and DYS-PAP (P < 0.0001) values, but lower CH (P = 0.001), global longitudinal (P = 0.005), radial (P = 0.03), and circumferential strain (P = 0.01) than those with mild MR. Receiver operating characteristic analysis was performed to assess the utility of DYS-PAP to predict moderate or moderate-to-severe functional MR. A DYS-PAP value >30 ms predicted moderate-to-severe MR with 85% sensitivity and 87% specificity [area under the curve: 0.897, 95% confidence interval (CI): 0.781–0.999, P < 0.0001]. Logistic regression analysis revealed that DYS-PAP (odds ratio: 3.2, 95% CI: 1.22–47.7, P = 0.037) was the only independent predictor of moderate or moderate-to-severe functional MR.

Conclusion
DYS-PAP is correlated with functional MR in non-ischaemic DCM patients with sinus rhythm. A DYS-PAP cut-off value of 30 ms is a useful tool to identify patients with moderate-to-severe functional MR.

Keywords
Papillary muscle dyssynchrony • Mitral regurgitation • Dilated cardiomyopathy

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**Introduction**

Functional mitral regurgitation (MR) is associated with decreased survival in patients with dilated cardiomyopathy (DCM). The suggested mechanisms for functional MR in DCM are the decrease in the transmitral pressure force which impairs effective mitral valve closure, the geometrical changes in the mitral annulus, papillary muscle, and mitral valve, and the dyssynchronous left ventricular (LV) and papillary muscle contractions. Cardiac resynchronization therapy (CRT) reduces the amount of functional MR in patients with LV systolic failure. The reduction in the amount of functional MR has been associated with the improved coordination of the papillary muscular contractions following CRT. However, the cut-off value to identify significant papillary muscle dyssynchrony is still unclear. Two-dimensional (2D) speckle-tracking imaging enables the angle-independent assessment of multidirectional LV strain and differentiates myocardial segments with active contraction from segments that are passively tethered. In our study, we investigated the impact of papillary muscle dyssynchrony in the prediction of significant functional MR with 2D speckle-tracking strain analysis in non-ischaemic DCM patients.

**Methods**

The study population was selected from the patients with non-ischaemic DCM who were evaluated in Kartal Kosuyolu Heart Education and Research Hospital cardiology outpatient clinic between December 2008 and October 2009. All patients who met the inclusion criteria were asked to participate in the study, and the ones who accepted to participate were enrolled prospectively. Patients with organic mitral valve disease that may cause MR (rheumatic or degenerative heart valve disease, mitral annular calcification, mitral valve prolapse, chordae tendinea rupture), history of acute coronary syndrome, ischaemic ECG findings, significant coronary artery disease in coronary angiography (>50% luminal stenosis), permanent pacemakers, and chronic kidney disease (patients with Stage 3 chronic kidney disease) were excluded from the study. All patients were evaluated carefully for their functional capacities. Twelve-lead ECGs were obtained (0.5–150 Hz, 25 mm/s, 10 mm/mV) and each patient had a coronary angiogram within the last 6 months prior to their enrolment in the study. Local Ethics Committee approved this cross-sectional study.

Standard echocardiographic evaluations were performed using a commercially available system (Vivid-7; GE Vingmed Ultrasound AS, Horten, Norway). Data acquisition was performed with a 3.5 MHz transducer at a depth of 16 cm in the parasternal and apical views (standard parasternal short-axis from mid-ventricular level, apical long-axis, two-chamber, and four-chamber images). Standard M-mode, 2D, and colour-coded TDI images were obtained during breath hold, stored in cine loop format from three consecutive beats, and transferred to a workstation for further offline analysis (EchoPAC 6.1; GE Vingmed Ultrasound AS). Cardiac dimensions were measured according to the guidelines of the European Society of Echocardiography and LVEF was calculated by the biplane Simpson’s method. The quantification of functional MR was performed using the proximal isovelocity surface area method as described previously. The effective regurgitant orifice area (ERO, cm²) and the regurgitant volume (Reg Vol, mL) were used as variables expressing the severity (mild MR: Reg Vol < 20 mL/beat or ERO < 0.20 cm²; moderate MR: Reg Vol = 20–39 mL/beat or ERO = 0.20–0.29 cm²; moderate-to-severe MR: Reg Vol = 40–59 mL/beat or ERO = 0.30–0.39 cm²; severe MR: Reg Vol > 60 mL/beat or ERO > 0.40 cm²).

The configuration of mitral leaflets was evaluated in the parasternal long-axis and apical four-chamber views. Mitral annulus diameter was measured in mid-systole from the base of mitral anterior leaflet to the base of mitral posterior leaflet in each view. Measurement of the coaptation height (CH) was performed by calculating the distance between mitral leaflet tips and annulus line in mid-systole in apical four-chamber view. Tethering distance was calculated from apical four-chamber view for anterolateral papillary muscle (Tethering-AL) and from apical long-axis view for postero medial papillary muscle (Tethering-PM) by measuring the distance between the papillary muscle tip and the base of the mitral leaflet as described previously.

Multidirectional analysis of LV strain (in the radial, circumferential, and longitudinal directions) was performed using 2D speckle-tracking imaging as described previously. The assessment of global radial strain (GRS) and global circumferential strain (GCS) was performed...
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by applying 2D speckle-tracking imaging to the parasternal short-axis views of the LV. The mid-ventricular short-axis of the LV is divided into six segments, and the values of GRS and GCS are derived from the average of the six segmental peak systolic strain values. The assessment of longitudinal peak systolic strain was performed by applying 2D speckle-tracking imaging to the apical two- and four-chamber views of the LV. The LV is divided into six segments in each apical view. The values of global longitudinal strain (GLS) are derived from the average of the six segments. The average value of peak systolic longitudinal strain for each view is determined as averaged global longitudinal peak systolic strain for the complete LV.

LV dyssynchrony was also evaluated with 2D speckle-tracking radial strain imaging, as described previously. By applying 2D speckle-tracking radial strain imaging to mid-ventricular parasternal short-axis images, LV dyssynchrony was evaluated by measuring the time difference between the anteroseptal and posterolateral peak radial strain (DYS-radial).

The assessment of papillary muscles was performed by applying 2D speckle-tracking imaging to the apical four-chamber view for anterolateral papillary muscle and to the apical long-axis view for posteromedial papillary muscle. From an end-systolic single frame, the papillary muscle was traced on the endocardial cavity interface by a point-and-click approach from the tip to the base. Following the papillary muscle tracing, an automated tracking algorithm followed the papillary muscle from this single frame throughout the cardiac cycle. Further adjustment of the region of interest was performed to ensure that all of the papillary muscle was included. Segmental time–strain curves of systolic longitudinal strain for each papillary muscle were obtained. The average value of peak systolic longitudinal strain for each papillary muscle was determined as anterolateral papillary muscle longitudinal strain (ALP-LS) and posteromedial papillary muscle longitudinal strain. The beginning of the QRS complex was used as the reference point and the time to peak systolic longitudinal strain was quantified for each papillary muscle (Ts-PAP). For the assessment of papillary muscle systolic dyssynchrony, the difference in Ts-PAP between anterolateral and posteromedial papillary muscles was calculated.

Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were obtained after 20 min rest following the echocardiographic evaluation. Commercial NT-proBNP assays (Elecsys Roche Diagnostics) were used for plasma NT-proBNP level measurement.

Statistical analysis was performed using a statistical software program (SPSS for Windows, version 15.0; SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD, controlled for normally distribution by the Kolmogorov–Smirnov test. Comparison of more than two groups was performed by using the Kruskal–Wallis test with the Bonferroni correction and differences between any two groups were compared by Mann–Whitney U-test because of abnormal distribution. Categorical data between two or more groups were compared by the Pearson χ² test. The correlation of continuous variables were analysed by Pearson’s correlation analysis and categorical variables by Spearman’s correlation analysis. In order to determine the optimal DYS-PAP value in predicting functional MR higher than mild (Reg Vol > 20 mL/beat or ERO > 0.20 cm²), the closest value to the best specificity and sensitivity point on the receiver operating characteristic (ROC) curve was identified. Logistic regression analysis was used to identify the independent predictors of moderate or moderate-to-severe MR out of echocardiographic parameters. A value of P < 0.05 was considered significant.

Results

Study population included 11 women (30.5%) and 25 men (69.5%). Mean age was 45 ± 13. MR volume was negatively correlated with LVEF, mitral CH, GLS, and GCS, and positively correlated with ERO area, Log NT-proBNP, NYHA functional class, mitral annulus size, left atrial dimension, LV end-systolic dimension, ALP-LS, and DYS-PAP. There were no significant correlations between MR volume and other echocardiographic parameters (Table 1).

There were 15 patients with mild (41.6%), 16 patients with moderate (44.4%), and 5 patients with moderate-to-severe (14%) MR. There was no patient with severe MR in the study group. Papillary muscle dyssynchrony measurements were significantly different in the various MR levels (mild MR, median 22 ms; moderate MR, median 45 ms; moderate-to-severe MR, median 58 ms; χ²: 18.3, Figure 2). For the measurement of peak papillary muscle systolic strain timing, the beginning of the QRS complex was used as the reference point and the time to peak systolic longitudinal strain was quantified for each papillary muscle (Ts-PAP) (Figure 2). For the assessment of papillary muscle systolic dyssynchrony, the difference in Ts-PAP between anterolateral and posteromedial papillary muscles was calculated.

Figure 2 For the measurement of peak papillary muscle systolic strain timing, the beginning of the QRS complex was used as the reference point and the time to peak systolic longitudinal strain was quantified for each papillary muscle (Ts-PAP). For the assessment of papillary muscle systolic dyssynchrony, the difference in Ts-PAP between anterolateral and posteromedial papillary muscles was calculated.
The study population was divided into two subgroups according to the severity of functional MR. Fifteen (41.6%) patients with mild MR (Reg Vol < 20 mL/beat or ERO < 0.20 cm²) constituted the first group, and 21 (58.3%) patients with moderate or moderate-to-severe MR (Reg Vol > 20 mL/beat or ERO > 0.20 cm²) constituted the second group. Patients with higher degrees of MR (first group) had larger mitral annulus size (P = 0.02), Tethering-AL (P = 0.04), higher MR volume (P < 0.0001), and ERO area (P < 0.0001) values, but lower CH (P = 0.001), GLS (P = 0.005), GRS (P = 0.03), and GCS (P = 0.01) than those with mild MR (second group). Patients with higher degrees of functional MR also had significantly higher DYS-PAP (P < 0.0001) values than those with mild MR. Other clinical and echocardiographic parameters were not significantly different between the two groups (Table 2).

ROC analysis was performed to assess the utility of DYS-PAP to predict higher degrees of functional MR (Reg Vol > 20 mL/beat or ERO > 0.20 cm²). A DYS-PAP value > 30 ms predicted higher levels of functional MR with 85% sensitivity and 87% specificity [area under the curve: 0.897, 95% confidence interval (CI): 0.781–0.999, P < 0.0001] (Figure 3).

Logistic regression analysis was performed to determine the independent predictors of higher levels of functional MR (Reg Vol > 20 mL/beat or ERO > 0.20 cm²). Mitral annulus diameter, mitral CH, NYHA functional class (I–II vs. III–IV), GRS, and DYS-PAP (<30 vs. >30 ms) were the covariates included in the model. Logistic regression analysis revealed that DYS-PAP (odds ratio: 3.2, 95% CI: 1.22–47.7, P = 0.037) was the only independent predictor of higher levels of functional MR.

**Table 1** Correlation analysis between mitral regurgitant volume and biochemical, clinical, and echocardiographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERO area (mm²)</td>
<td>0.926</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log NT-proBNP</td>
<td>0.705</td>
<td>0.007</td>
</tr>
<tr>
<td>NYHA class I–II/III–IV</td>
<td>0.370</td>
<td>0.026</td>
</tr>
<tr>
<td>Annulus-PLax (cm)</td>
<td>0.36</td>
<td>0.020</td>
</tr>
<tr>
<td>Annulus-4C (cm)</td>
<td>0.247</td>
<td>0.152</td>
</tr>
<tr>
<td>CH (cm)</td>
<td>−0.543</td>
<td>0.001</td>
</tr>
<tr>
<td>Tethering-AL (cm)</td>
<td>0.320</td>
<td>0.065</td>
</tr>
<tr>
<td>Tethering-PM (cm)</td>
<td>0.212</td>
<td>0.229</td>
</tr>
<tr>
<td>LA (cm)</td>
<td>0.327</td>
<td>0.048</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>0.285</td>
<td>0.092</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>0.380</td>
<td>0.022</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>−0.357</td>
<td>0.032</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>−0.479</td>
<td>0.003</td>
</tr>
<tr>
<td>GRS (%)</td>
<td>−0.327</td>
<td>0.055</td>
</tr>
<tr>
<td>GCS (%)</td>
<td>−0.471</td>
<td>0.004</td>
</tr>
<tr>
<td>ALP-LS (%)</td>
<td>0.429</td>
<td>0.010</td>
</tr>
<tr>
<td>PMP-LS (%)</td>
<td>0.179</td>
<td>0.320</td>
</tr>
<tr>
<td>DYS-PAP (ms)</td>
<td>0.814</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ERO, mitral regurgitation effective regurgitant orifice area; CH, coaptation height; Tethering-AL, anterolateral papillary muscle tethering distance; Tethering-PM, posteromedial papillary muscle tethering distance; LA, left atrium diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain; ALP-LS, anterolateral papillary muscle longitudinal strain; PMP-LS, posteromedial papillary muscle longitudinal strain; DYS-PAP, papillary muscle dyssynchrony.

Discussion

Functional MR and intraventricular dyssynchrony are common findings in patients with heart failure and they are associated with a poor prognosis. The dysynchronous contractions of LV segments and papillary muscles are the leading causes of functional MR in these patients. Our study demonstrated that papillary muscle dyssynchrony was the independent predictor of moderate or moderate-to-severe MR in patients with non-ischaemic DCM.

The cut-off value to predict significant papillary muscle dyssynchrony is still unknown in the remodelled and spherisized myocardium. Most of the CRT studies about papillary muscle dyssynchrony have investigated the possible papillary muscle insertion regions on the LV in their radial and longitudinal strain analysis. In our recent publication, we used the TDI-based longitudinal strain of papillary muscles, and we reported that 60 ms cut-off value of the papillary muscle dyssynchrony predicted the MR volume >20 mL in patients with DCM. In patients with heart failure, lateral, posterior, and inferior myocardial segments are usually the most delayed ventricular segments. Papillary muscles are usually localized at the lateral and inferior segments which contract later than the other myocardial regions. Most of the studies on this topic reported different cut-off values and the optimal delay for CRT has been still unclear. Therefore, the cut-off levels for the prediction of papillary muscle dyssynchrony are required for better assessment of severity of MR and evaluation for CRT.

Two-dimensional speckle-tracking imaging provides angle-independent assessment of multidirectional LV strain and differentiates myocardial segments with active contraction from segments that are passively tethered. Two recent studies used radial strain analysis to assess the dyssynchrony at the papillary muscle insertion areas from the parasternal short-axis views. Both studies reported significant association between the dyssynchrony and improvement of MR following CRT. To our knowledge, our study is the first report investigating both papillary muscles with 2D speckle-tracking imaging strain analysis from the longitudinal axis. We found significant correlation between the functional MR degree and intraventricular mechanical dyssynchrony and echocardiographic parameters including the mitral valve geometry and configuration. However, we found that significant DYS-PAP was the only independent predictor of moderate or moderate-to-severe MR. The cut-off value for DYS-PAP (30 ms) has predicted the mitral Reg Vol > 20 mL or ERO area >0.20 cm² with high sensitivity and specificity. Hence, this value might be clinically useful in patient selection for CRT.

The beneficial effects of CRT are less clear in patients with ischaemic heart failure, severe MR, and LVEDD ≥ 75 mm. According to this study, a patient with non-ischaemic heart disease, less than moderate degree of MR, and an LV end-diastolic diameter <75 mm would have predicted the response to CRT.
with a probability of more than 90%. Cabrera-Bueno et al. demonstrated that the presence of severe MR at baseline was associated with a lack of response in reverse remodelling in patients with non-ischaemic DCM, although there was significant improvement in MR and intraventricular dyssynchrony. Therefore, it is speculated that the maximum benefit of CRT on secondary MR and on LV remodelling seems to be peculiar in patients with at least moderate-to-severe MR; however, without severe MR. In addition, persistence of MR after CRT was associated with worse clinical outcomes, greater incidence of arrhythmic events, and less reverse remodelling. In this study, we found that DYS-PAP ≥ 30 ms independently predicted the patients with moderate or moderate-to-severe functional MR. This information could be clinically important to determine the patients with DCM and functional MR who would benefit from CRT.

Limitations

The major limitation of our study is the lack of follow-up data for the study population. Most of the patients were in NYHA functional class II and had narrow QRS intervals. CRT implantation was performed in 3 of 36 patients, and this number is too small for analysis of CRT outcomes. Higher degrees of MR despite narrow QRS intervals and minimal papillary muscle dyssynchrony in this group suggest potential beneficial effect of CRT. Hence, re-analysis of our hypothesis with different echocardiographic methods and larger number of patients might confirm or refute our hypothesis.

Conclusion

Papillary muscle dyssynchrony is correlated with functional MR in non-ischaemic DCM patients with sinus rhythm. A DYS-PAP cut-off value of 30 ms is a useful tool to identify patients with...
moderate or moderate-to-severe functional MR. Appropriate interpretation of papillary muscle dyssynchrony may change the treatment options in these patients.

Conflict of interest: none declared.

References


