Incremental value of global systolic dyssynchrony in determining the occurrence of functional mitral regurgitation in patients with left ventricular systolic dysfunction

Yu-Jia Liang1,3, Qing Zhang1,3, Fang Fang1,3, Alex Pui-Wai Lee1,3, Ming Liu1,3, Bryan Ping-Yen Yan1,3, Yat-Yin Lam1,3, Gary Chin-Pang Chan1,3, and Cheuk-Man Yu1,2,3*

1Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, Peoples’ Republic of China; 2The Translational Medicine R&D Center, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Peoples’ Republic of China; and 3Heart Education and Research Training (HEART) Centre, Institute of Vascular Medicine, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, Peoples’ Republic of China

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Aims

The aim of this study was to assess the contribution of left ventricular (LV) systolic dyssynchrony to functional mitral regurgitation (MR).

Methods and results

Patients (n = 136) with LV systolic dysfunction (ejection fraction < 50%) and at least mild MR were prospectively recruited. The effective regurgitant orifice area (EROA) was assessed by the proximal isovelocity surface area method. Left ventricular global systolic dyssynchrony [the maximal difference in time to peak systolic velocity among the 12 LV segments (Ts-Dif)] and regional systolic dyssynchrony (the delay between the anterolateral and posteromedial papillary muscle attaching sites) were assessed by tissue Doppler imaging. Left ventricular global and regional remodelling, systolic function, indices of mitral valvular and annular deformation were also measured. The size of the EROA correlated with the degrees of mitral deformation, LV remodelling, systolic function, and systolic dyssynchrony. By multivariate logistic regression analysis, the mitral valve tenting area (OR = 1.020, P < 0.001) and the Ts-Dif (OR = 1.011, P = 0.034) were independent determinants of significant functional MR (defined by EROA ≥ 20 mm²). From the receiver-operating characteristic curve, the tenting area of 2.7 cm² (sensitivity 83%, specificity 82%, AUC 0.86, P < 0.001) and the Ts-Dif of 85 ms (sensitivity 66%, specificity 72%, AUC 0.74, P < 0.001) were associated with significant functional MR. The assessment of Ts-Dif showed an incremental value over the mitral valve tenting area for determining functional MR (χ² = 53.92 vs. 49.11, P = 0.028).

Conclusion

This cross-sectional study showed that LV global, but not regional systolic dyssynchrony, is a determinant of significant functional MR in patients with LV systolic dysfunction, and is incremental to the tenting area that is otherwise the strongest factor for mitral valve deformation.

Keywords

Mitral regurgitation • Dyssynchrony • Systolic dysfunction

Introduction

Functional mitral regurgitation (MR) is frequently observed in patients with congestive heart failure, and carries an adverse prognosis.1,2 The pathogenesis of functional MR involves multiple factors, but the major mechanism is believed to be the increased mitral leaflet tethering due to the outward displacement of the two papillary muscles caused by global and regional left ventricular (LV) remodelling.3–6 Other factors such as the decreased LV closing force and dysfunction or deformation of the mitral annulus are also involved.5–8

* Corresponding author. Tel: +86 852 2632 3594, Fax: +86 852 2637 5643, Email: cmyu@cuhk.edu.hk

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Left ventricular systolic dyssynchrony has been described in heart failure population with a high prevalence, which reflects an uncoordinated contraction of the LV segments and implicates a poor prognosis.\textsuperscript{9,10} Recent studies have shown that reduction in functional MR by cardiac resynchronization therapy (CRT) was associated with improvement in LV regional systolic dyssynchrony from the segments bearing the two papillary muscles.\textsuperscript{11,12} Further studies suggested that regional dyssynchrony could be a potential contributor to the severity of functional MR.\textsuperscript{13,14} However, the contribution of LV global systolic dyssynchrony has not been evaluated as a factor. Therefore, the objective of this study was to assess the contribution of LV systolic dyssynchrony to functional MR in patients with LV systolic dysfunction, and to examine whether LV global or regional dyssynchrony will have an incremental predictive value for significant functional MR in addition to other relevant factors.

**Methods**

**Patients**

From January 2007 to September 2008, this study enrolled a cohort of 182 consecutive patients with the LV ejection fraction <50% measured by biplane Simpson’s method\textsuperscript{15} who were followed up at 3 or 6 months after an admission for acute decompensated heart failure. Among them, 35 patients were excluded if they had organic mitral valve disease, clinical or echocardiographic evidence of other cardiac diseases, previous implantation of any type of pacemaker, history of recent myocardial infarction (<30 days), atrial fibrillation or other arrhythmias. Another 11 patients with or without trivial MR in whom the proximal isovelocity surface area (PISA) method could not be used for quantification were also excluded. Consequently, the study population consisted of 136 patients with impaired LV systolic function and at least mild functional MR.

**Echocardiography**

The standard transthoracic echocardiography with tissue Doppler imaging (TDI) was performed in all patients (Vivid 7, Vingmed-General Electric, Horton, Norway) at 3 or 6 months after the initial admission for acute decompensated heart failure. The assessments of MR severity, LV global and regional remodelling, LV systolic function, mitral valve deformation, and LV global and regional systolic dyssynchrony were performed by offline analysis (EchoPac PC 7.0.0, Vingmed-General Electric, Horton, Norway).

The degree of functional MR was assessed by calculating the effective regurgitant orifice area (EROA) using the PISA method.\textsuperscript{16} For the assessment of LV global remodelling, the left ventricular end-systolic volume (LVESV) and the left ventricular end-diastolic volume (LVEDV) were measured by the biplane Simpson’s method.\textsuperscript{15} Left ventricular end-systolic and end-diastolic cavity length and mid-cavity width were measured at the apical four-chamber view and sphericity indices at end-systole and end-diastole were calculated to assess LV geometry.\textsuperscript{17} The LV ejection fraction\textsuperscript{15} and LV peak positive dP/dt (LV + dP/dt)\textsuperscript{18} were measured to evaluate LV systolic function. Left ventricular regional remodelling was assessed by papillary-fibrous distance, which was measured from the posteromedial papillary muscle head to the intervalvular fibrosa in the apical long-axis view.\textsuperscript{5} Mitral valve deformation was assessed by the tenting area and the tenting height from the parasternal long-axis view at mid-systole.\textsuperscript{6}

The maximal and minimal mitral annular dimensions were measured and the maximal and minimal mitral annular areas (MAA) were calculated. Mitral annular contractility was calculated by the percentage of change in MAA during the cardiac cycle, as \((\text{maximal MAA} - \text{minimal MAA})/\text{maximal MAA} \times 100\%\).

Left ventricular systolic mechanical dyssynchrony was assessed by two-dimensional colour-coded TDI in the three apical views (i.e. apical four-chamber, two-chamber, and apical long-axis views). The assessment was performed offline in separate sessions by trained sonographers who were blinded to the severity of MR or degree of LV remodelling. Myocardial velocity curves were reconstituted offline using the six-basal, six-mid-segmental model in the LV as previously described.\textsuperscript{17} The time to the myocardial peak systolic velocity during the ejection phase (Ts) was measured in each segment.\textsuperscript{19} Left ventricular global systolic dyssynchrony was assessed by the maximal difference of Ts among the 12 LV segments (Ts-Dif).\textsuperscript{20} Left ventricular regional dyssynchrony was assessed by the absolute difference in Ts between the mid-lateral and mid-inferior segments, representing the delay between the anterolateral and posteromedial papillary muscle attaching sites (APM–PPM delay).

**Statistical analysis**

The statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 13.0. A P-value <0.05 (two-sided) was considered statistically significant. Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. The unpaired t-test or the Pearson $\chi^2$ test was used when appropriate to compare between patients with and without significant functional MR. Pearson correlation analysis was employed to examine the relationship between EROA and other clinical or echocardiographic parameters. Receiver-operating characteristics (ROC) curve was constructed to evaluate the contributions of valvular tenting and dyssynchrony to the degree of MR and to define the cut-off values for determining significant functional MR. Determinants of significant functional MR were identified by univariate logistic regression followed by forward stepwise multivariate logistic regression, with P-value <0.05 as the threshold for inclusion in the multivariable model.

**Results**

**Patient baseline characteristics**

The mean age of patients was 66 ± 12 years and there were 98 (72.1%) males. The mean ejection fraction was 30 ± 9% (range 13–48%). The aetiology of heart failure was ischaemic in 72 (52.9%) patients and non-ischaemic in 64 (47.1%) patients. Forty-six out of the 72 (63.9%) patients with ischaemic aetiology had a history of revascularization (percutaneous coronary intervention or coronary artery bypass grafting) procedures. An ischaemic aetiology was confirmed by a documented myocardial infarction and/or abnormal coronary angiography with ≥70% stenosis in at least one coronary artery. Patients with non-ischaemic aetiology had normal coronary angiography, and among them, 58 patients were suffering from idiopathic dilated cardiomyopathy, one patient had hypertensive heart disease, and five patients had alcoholic cardiomyopathy. The mean QRS duration was 109 ± 28 ms, though 42 (30.9%) patients had a prolonged QRS complex of >120 ms. Medications included angiotensin-converting enzyme inhibitors or angiotensin receptors blocker in 110 (80.9%).
β-blockers in 96 (70.6%), diuretics in 87 (64.0%), nitrates in 42 (30.9%), spironolactone in 21 (15.4%), and digoxin in 11 (8.1%) patients.

### Severity of functional mitral regurgitation and its determinants

In the 136 patients who had measurable MR by the PISA method, the mean EROA was 19 ± 13 mm² (ranged from 2 to 61 mm²). By using the EROA ≥20 mm² as the cut-off value for clinically significant MR as previously validated, 47 (35%) patients had significant functional MR.

Comparisons were performed between patients with significant functional MR (group 1, n = 47) and those without (group 2, n = 89, 65%). There was no significant difference in baseline demographics between the two groups, except a lower systolic blood pressure in group 1 (Table 1). With respect to echocardiographic parameters of LV remodelling and function, group 1 had significantly a larger LVEDV (P = 0.031) and LVESV (P = 0.020), a greater end-systolic and end-diastolic LV short-axis dimension (both P < 0.05), a lower LV end-diastolic sphericity index (P = 0.021), as well as greater papillary-fibrosa distance (P < 0.001) and lower LV + dP/dt (P < 0.001). Patients in group 1 also had a larger tenting area (P < 0.001), a greater tenting height (P < 0.001) as well as more severe LV global (P < 0.001), and regional (P = 0.001) systolic dyssynchrony (Table 2). In addition, it was observed that the size of the EROA correlated with LV remodelling, LV contractility, mitral valvular and annular deformation, as well as LV global and regional systolic dyssynchrony (Table 2). Of note, the correlation between EROA and LV global systolic dyssynchrony (Ts-Dif) was closer than that of EROA and regional dyssynchrony (APM–PPM delay).

### Discussion

In the current study, we have demonstrated that in patients with LV systolic dysfunction, assessment of global LV systolic dysynchrony provides an incremental value to the mitral valve tenting area in determining the presence of significant functional MR.

### Mitral valve deformation in prediction of functional mitral regurgitation

Several interrelated geometric and haemodynamic factors will lead to functional MR. Among them, mitral valve deformation caused by subvalvular tethering is considered to be the main determinant of MR severity. In previous studies, multiple parameters had been proposed for the assessment of mitral valve deformation, such as tenting area, tenting height, as well as leaflet concavity, which were found to be closely correlated with the degree of functional MR. In the present study, we also observed a significant correlation between EROA and mitral valve deformation. The imbalance between mitral valve tethering and closing forces is a major factor in functional MR. Consequently, we investigated a number of parameters closely related to these two determinants (shown in Table 2) for their association with EROA in order to identify those most significant. In addition to mitral valve deformation, other variables were also included representing LV global and regional remodelling, LV contractility, mitral annular shape, as well as systolic dyssynchrony. Among these multiple echocardiographic parameters assessed, the mitral valve tenting area had the highest...
Table 2  Echocardiographic characteristics of patients with and without significant functional mitral regurgitation

<table>
<thead>
<tr>
<th>Comparison between groups</th>
<th>EROA ≥ 20 mm² (n = 47)</th>
<th>EROA &lt; 20 mm² (n = 89)</th>
<th>P-value</th>
<th>Correlation with EROA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global LV remodelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>185 ± 67</td>
<td>162 ± 54</td>
<td>0.031</td>
<td>0.311</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>135 ± 60</td>
<td>114 ± 45</td>
<td>0.020</td>
<td>0.346</td>
</tr>
<tr>
<td>End-systolic LV cavity length, cm</td>
<td>8.1 ± 1.0</td>
<td>7.9 ± 0.9</td>
<td>0.312</td>
<td>0.866</td>
</tr>
<tr>
<td>End-systolic LV cavity width, cm</td>
<td>5.0 ± 1.0</td>
<td>4.6 ± 0.8</td>
<td>0.016</td>
<td>0.290</td>
</tr>
<tr>
<td>End-systolic LV sphericity index</td>
<td>1.67 ± 0.27</td>
<td>1.76 ± 0.26</td>
<td>0.066</td>
<td>-0.267</td>
</tr>
<tr>
<td>End-diastolic LV cavity length, cm</td>
<td>8.9 ± 0.9</td>
<td>8.6 ± 0.9</td>
<td>0.521</td>
<td>0.149</td>
</tr>
<tr>
<td>End-diastolic LV cavity width, cm</td>
<td>5.6 ± 0.8</td>
<td>5.3 ± 0.7</td>
<td>0.015</td>
<td>0.317</td>
</tr>
<tr>
<td>End-diastolic LV sphericity index</td>
<td>1.57 ± 0.19</td>
<td>1.65 ± 0.18</td>
<td>0.021</td>
<td>-0.252</td>
</tr>
<tr>
<td>Regional LV remodelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Papillary-fibrosa distance, cm</td>
<td>3.8 ± 0.4</td>
<td>3.4 ± 0.4</td>
<td>&lt;0.001</td>
<td>0.450</td>
</tr>
<tr>
<td>LV contractility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>28 ± 9</td>
<td>31 ± 8</td>
<td>0.110</td>
<td>-0.272</td>
</tr>
<tr>
<td>LV + dP/dt, mmHg/s</td>
<td>674 ± 153</td>
<td>793 ± 207</td>
<td>0.001</td>
<td>-0.371</td>
</tr>
<tr>
<td>Mitral valvular deformation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenting area, cm²</td>
<td>3.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
<td>&lt;0.001</td>
<td>0.632</td>
</tr>
<tr>
<td>Tenting height, cm</td>
<td>1.4 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>&lt;0.001</td>
<td>0.476</td>
</tr>
<tr>
<td>Annular factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic mitral annular area, cm²</td>
<td>7.0 ± 1.3</td>
<td>6.8 ± 1.1</td>
<td>0.397</td>
<td>0.220</td>
</tr>
<tr>
<td>Systolic mitral annular area, cm²</td>
<td>6.4 ± 1.4</td>
<td>6.1 ± 1.1</td>
<td>0.207</td>
<td>0.263</td>
</tr>
<tr>
<td>Mitral annular contractility, %</td>
<td>9 ± 5</td>
<td>11 ± 6</td>
<td>0.083</td>
<td>-0.206</td>
</tr>
<tr>
<td>LV systolic dysynchrony</td>
<td></td>
<td></td>
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<tr>
<td>Ts-Dif, ms</td>
<td>108 ± 52</td>
<td>68 ± 41</td>
<td>&lt;0.001</td>
<td>0.376</td>
</tr>
<tr>
<td>APM–PPM delay, ms</td>
<td>71 ± 47</td>
<td>46 ± 39</td>
<td>0.001</td>
<td>0.291</td>
</tr>
</tbody>
</table>

APM–PPM delay, the absolute difference in time to peak systolic velocity between the mid-lateral and mid-inferior left ventricular segments; EROA, effective regurgitant orifice area; LV, left ventricle; Ts-Dif, the maximal difference in time to peak systolic velocity among the 12 LV segments.

Table 3  Univariate and multivariate logistic regression analyses to examine for determinants of significant functional mitral regurgitation

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>CI</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>0.982</td>
</tr>
<tr>
<td>Heart failure etiology, ischaemic</td>
<td>0.686</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>1.008</td>
</tr>
<tr>
<td>LV + dP/dt, mmHg/s</td>
<td>0.997</td>
</tr>
<tr>
<td>Tenting area, mm²</td>
<td>1.023</td>
</tr>
<tr>
<td>Papillary-fibrosa distance, mm</td>
<td>1.248</td>
</tr>
<tr>
<td>Systolic mitral annular area, mm²</td>
<td>1.002</td>
</tr>
<tr>
<td>Ts-Dif, ms</td>
<td>1.019</td>
</tr>
<tr>
<td>APM–PPM delay, ms</td>
<td>1.014</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
correlation coefficient of 0.632 with the EROA. In fact, the mitral valve tenting area appeared to be the only independent determinant of significant functional MR among all the geometrical measurements in dimensions or volumes. The majority of other variables with weak correlations may not be independent determinants, but could contribute to functional MR by interacting with several factors through a common pathway leading to an increased tenting area.

Left ventricular systolic dyssynchrony as a new determinant of functional mitral regurgitation

Left ventricular intraventricular systolic dyssynchrony is increasingly recognized as an important mechanism in patients with systolic dysfunction. Apart from its prognostic importance, it is a fundamental mechanism in CRT and LV dyssynchrony may also play a role in the pathophysiology of functional MR in patients with LV systolic dysfunction or heart failure. In earlier studies, this relationship was reflected indirectly by the observation that more severe functional MR was associated with longer QRS duration. By using TDI-derived myocardial velocities, a recent study has suggested that systolic dyssynchrony was associated with the severity of functional MR only in the subgroup of 35 non-ischaemic subjects, but not the whole cohort of 74 patients with systolic dysfunction. However, this study was unable to differentiate the relative importance of global or regional LV dyssynchrony as eight segments adjacent to papillary muscles were measured thus including possible contribution of both factors. Another study used TDI-derived strain of the two papillary muscles in 32 patients with non-ischaemic dilated cardiomyopathy and concluded that regional dyssynchrony and LV chamber sphericity were independent determinants of functional MR, though surprisingly neither mitral valve tenting area nor coaptation distance were significant.

In the current study with a larger sample size, we assessed in detail the potential determinants of significant functional MR including the parameters of both global (Ts-Dif) and regional (APM–PPM delay) LV systolic dyssynchrony, with demographic variables, the aetiology of LV systolic dysfunction, indices of global and regional LV remodelling, as well as parameters of mitral valvular and annular deformation. In addition to the mitral valve tenting area, LV global, but not regional dyssynchrony was an independent determinant of significant functional MR confirmed by both univariate and multivariate analyses. Furthermore, by the use of stepwise forward logistic regression analysis, an incremental value of the Ts-Dif to tenting area (both as continuous variables) in determining the severity of MR was confirmed. To assess further the relationship between these two factors, we used ROC curves to define the cut-off values for the Ts-Dif and tenting area, and then studied the influence of the combination of these two factors on functional MR. From our study, we found that a cut-off value of Ts-Dif ≥ 85 ms predicted the development of functional MR in both ischaemic and non-ischaemic patients with a relatively good sensitivity and specificity, though at a lesser degree compared with the tenting area ≥ 2.7 cm². Of note, this cut-off indicates only a moderate level of intraventricular dyssynchrony, when compared with the previously published value of 100 ms, which predicts a favourable response after CRT for advanced heart failure patients. Interestingly, there was no difference in QRS duration between the patients with and without significant functional MR. Therefore, it appears that the development of functional MR is not determined by the uncoordinated motion generated from the two papillary muscles, but rather different LV segments with dysynchronous motion in concert contribute to the development of functional MR.
Thus, LV systolic dyssynchrony may cause the increase in functional MR by several pathways. Firstly, the presence of LV global systolic dyssynchrony may decrease the efficiency of LV contraction during systole, thus decrease LV closing force acting on the mitral leaflets. Secondly, dyssynchronous contraction of the papillary muscle insertion sites at the LV free wall may induce geometric distortion of the mitral valve apparatus. Lastly, dyssynchronous contraction of the LV basal segments may render a non-simultaneous contraction of the papillary muscles and adjacent LV walls, resulting in uneven timing of leaflet coaptation. Therefore, assessment of global LV dyssynchrony appears superior to regional dyssynchrony in determining significant functional MR as the latter is only one of the few factors being measured by the former parameter.

Clinical implications

Our results are relevant to the outcome of CRT that has been suggested to reduce the severity of functional MR both immediately after device implantation and in the long-term follow-up. Acute reduction in functional MR after CRT by improvement of LV systolic dyssynchrony was previously described. Pre-pacing mechanical dyssynchrony was demonstrated as a determinant of MR improvement after CRT. Patients with significant MR reduction were found to have more mechanical dyssynchrony before device implantation, when compared with those with no MR improvement. Therefore, it is postulated that CRT would be an alternative therapeutic option for significant functional MR in heart failure when surgical valvular repair or replacement as a current standard treatment inappropriate.

Study limitations

Functional MR is a dynamic condition in patients with LV systolic dysfunction, which may vary with time due to the changes in LV preload, afterload, remodelling, dyssynchrony, and other clinical status. However, this cross-sectional study only provided a brief snapshot of how the severity of functional MR related to LV dyssynchrony and other clinical or echocardiographic factors at baseline. The study would be strengthened by the addition of outcome data and by the evidence showing progression of functional MR together with progressive LV global or regional remodelling and probably increasing LV dyssynchrony.

Although the present study emphasizes the pathophysiological importance of functional MR in heart failure patients and suggests a therapeutic role of CRT in this special population, the information whether the severity of functional MR and its specific underlying pathology determines the treatment strategy (CRT alone,
surgery alone or both) are not provided and not answered. Future studies with a larger sample size and prospective design are needed.

Conclusions

In conclusion, our study showed that in patients with LV systolic dysfunction, significant functional MR was a relatively common condition. Significant functional MR was determined not only by mitral valve tenting area, but also the degree of global LV systolic dyssynchrony. Furthermore, the cut-off value of Ts-Dif ≥85 ms provided an incremental predictive value to the mitral valve tenting area ≥2.7 cm². Nevertheless, the values of these parameters need to be further validated by more clinical studies.

Funding

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Conflict of interest: none declared.

References

1. Trichon BH, Felker GM, Shaw LK, Cabell CH, O’Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538–543.


