Correlation between Mitral Regurgitation and Myocardial Mechanical Dyssynchrony and QRS Duration in Patients with Cardiomyopathy

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Abstract

Background: Several competing geometric and hemodynamic factors are suggested as contributing mechanisms for functional mitral regurgitation (MR) in heart failure patients. We aimed to study the relationships between the severity of MR and the QRS duration and dyssynchrony markers in patients with ischemic or dilated cardiomyopathy.

Methods: We prospectively evaluated 251 heart failure patients with indications for echocardiographic evaluation of possible cardiac resynchronization therapy. All the patients were subjected to transthoracic echocardiography and tissue Doppler imaging to evaluate the left ventricular (LV) synchronicity. The patients were divided into two groups according to the severity of MR: ≤ mild MR and ≥ moderate MR. The effects of different dyssynchrony indices were adjusted for global and regional left ventricular remodeling parameters.

Results: From the 251 patients (74.5% male, mean age = 53.38 ± 16.68 years), 130 had ≤ mild MR and 121 had ≥ moderate MR. There were no differences between the groups regarding the mean age, frequency of sex, and etiology of cardiomyopathy. The LV systolic and diastolic dimensions were greater in the patients with ≥ moderate MR (all p values < 0.001). Among the different echocardiographic factors, the QRS duration (150.75 ± 34.66 vs. 126.77 ± 29.044 ms; p value = 0.050) and interventricular mechanical delay (41.60 ± 29.50 vs. 35.00 ms ± 22.01; p value = 0.045) were significantly longer in the patients with ≤ mild MR in the univariate analysis. After adjusting the effect of these parameters on the severity of MR for the regional and global LV remodeling parameters, no significant impact of the QRS duration and dyssynchrony indices was observed.

Conclusion: Our results showed that the degree of functional MR was not associated with the QRS duration and inter- and intraventricular dyssynchrony in our patients with cardiomyopathy. No association was found between the severity of MR and the ischemic or dilated etiology for cardiomyopathy.

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**Introduction**

Functional mitral regurgitation (MR) is associated with exacerbatation in clinical symptoms and poor prognosis and probably induces additional adverse ventricular remodeling through volume overload in heart failure patients.\(^1\)\(^-\)\(^3\) Several competing geometric and hemodynamic factors such as abnormalities in the left ventricular (LV) volumes, function, and shape as well as the LV dyssynchrony and the QRS duration are among the suggested contributing mechanisms for determining the severity of functional MR in heart failure patients.\(^4\)\(^-\)\(^7\) There is some evidence that this relationship may vary in patients with idiopathic (DCM) and ischemic (ICM) dilated cardiomyopathy.\(^4\)\(^-\)\(^6\)

On these grounds, the aim of the present study was to examine the relationships between the severity of functional MR and the QRS duration and intra- and interventricular dyssynchrony in a group of patients with cardiomyopathy and investigate the effect of the etiology of cardiomyopathy in this regard.

**Methods**

Between January 2007 and March 2010, we prospectively evaluated 251 heart failure patients (74.5% male, mean age \(= 53.38 \pm 16.68\) years) with indications for cardiac resynchronization therapy who were referred to one of the echocardiography clinics in Tehran Heart Center, Tehran, Iran, for a pre-procedural echocardiographic evaluation. The inclusion criteria were comprised of the New York Heart Association (NYHA) classes II–III, refractory heart failure, and LV ejection fraction (LVEF) \(\leq 35\%\). Patients with previous pacemaker implantation were excluded from the study. All the patients underwent complete resting conventional echocardiography and tissue Doppler imaging (TDI) for the evaluation of the extent of the LV dyssynchrony. The etiology was diagnosed as ischemia if the patients had either evidence of previous myocardial infarction or angiographic evidence of significant coronary artery disease (at least narrowing \(\geq 50\%\) in one epicardial coronary artery) with corresponding wall motion abnormality. This study was reviewed and approved by our institutional review board.

Standard twelve-lead electrograms were acquired at a paper speed of 25 mm/s and a scale of 10 mm/mV. The measurement of the QRS duration (recorded from the surface leads, demonstrating the greatest values) was performed by an experienced observer.

Conventional echocardiographic studies, comprising complete two-dimensional (2D) transthoracic echocardiography, M-mode, pulsed, and continuous-wave Doppler with color-flow imaging, were performed using a commercially available ultrasonographic system (VIVID 7, Vingmed GE, Horten, Norway with a 3.5-MHz transducer). Standard echocardiography was performed with the subjects in the partial left decubitus position. The severity of MR was graded on a four-point scale\(^8\): I (mild), jet area/LA area < 15%; II (moderate), jet area/LA area = 15-30%; III (moderately severe), jet area/LA area = 35-50%; and IV (severe), jet area/LA area > 50. The LV end-diastolic and end-systolic volumes (bi-plane Simpson disc method) and diameters were measured. Efforts were made to record the apical four-chamber view in inspiration to optimize long-axis measurement.

The LV wall motion score index (WMSI) was calculated as the mean score in a sixteen-segment model of the LV using 2D images, in which each segment was given a score in the range 1-4, using 1 = normal wall motion, 2 = hypokinetic wall motion, 3 = akinetic, and 4 = paradoxical wall motion (dyskinesia).

TDI systolic synchronicity was performed according to the American Society of Echocardiography (ASE) expert consensus statement for echocardiography for cardiac resynchronization therapy\(^9\) and was assessed via TDI using the apical views (four-chamber, two-chamber, and long-axis) of the LV as was previously described with adjustments of the filter frequency, gain settings, pulse repetition frequency, and color saturation. At least three consecutive beats were stored, and the images were digitally stored for off-line analysis. The following twelve segments were interrogated: septal; lateral; anterior; inferior; anteroseptal; and posterior walls at both basal and middle levels. The timing of the systolic events was evaluated by measuring TDI in each LV segment with reference to the onset of the QRS complex.

Myocardial velocity curves were constructed with the TDI images simultaneously, when necessary, to confirm the pattern of myocardial motion. The time-to-peak systolic velocity (Ts) and the time from the onset of the QRS complex to the maximum positive velocity during the ejection period were measured. If a positive velocity was not observed, the segment was excluded from the study. If there were multiple peaks in the ejection period with the same velocity, the earliest peak was chosen.\(^10\)

The definitions of the dysynchrony indices measured in this study were reported in detail in our previous study.\(^11\) In summary, the interventricular dysynchrony was assessed by measuring the opening and closing times of the aortic and pulmonic valves using the systolic blood flow by pulsed Doppler, with the sample volume placed at the level of the aortic and pulmonic annulus. The aortic pre-ejection time was measured from the beginning of the QRS complex to the beginning of the aortic flow velocity curve recorded by pulsed-wave Doppler in the apical view. Similarly, the pulmonary pre-ejection time was measured from the beginning of the QRS complex to the beginning of the pulmonary flow velocity curve recorded in the left parasternal short-axis view. The difference between the two
values determined the interventricular mechanical delay (IVMD). Cardiac synchronicity was assessed through the measurements of time intervals, obtained in twelve LV segments. The following intraventricular indices were calculated: All segments delay (Ts-all-delay): delay between the shortest and longest Ts in twelve LV segments Basal segments delay (Ts-basal-delay): delay between the shortest and longest Ts in LV basal segments All segments standard deviation (Ts-all-SD): SD of the time-to-peak myocardial systolic velocity of twelve LV basal and mid segments Basal segments SD: (Ts-basal-SD) SD of the time-to-peak myocardial systolic velocity of six LV basal segments Mid- and basal-septal-lateral delay: the maximum delay between the peak systolic velocities between the septum and the lateral wall in the mid and basal levels Mid- and basal-antero-septal-posterior delay: the maximum delay between the peak systolic velocities between the anteroseptal and the posterior walls in the mid and basal levels Mid- and basal-anterior-inferior delay: the maximum delay between the peak systolic velocities between the anterior and the inferior walls in the mid and basal levels Mid- and basal-septal-posterior delay: the maximum delay between the peak systolic velocities between the septum and the posterior wall in the mid and basal levels. Because of the importance of the four anterior, lateral, inferior, and posterior LV walls in supporting the papillary muscle attachment, we included the delay between the shortest and longest Ts in these eight LV segments (Ts-eight segments delay) and the SD of the Ts in eight segments (Ts-eight segments SD) in the anterior, lateral, inferior, and posterior walls at both basal and mid-levels. The data are expressed as mean ± standard deviation (SD) or percentages. For these analyses, the normality of the residue hypothesis was tested using the Kolmogorov–Smirnov test. The chi-squared or the Fisher Exact test was employed to compare the proportions. The continuous variables were compared using the two-tailed Student t-test for the parametric and the Mann-Whitney test for the nonparametric variables as appropriate quantitative variables. Then, in a multiple logistic regression analysis, the effect of the dyssynchrony indices on the MR severity was explored by adjusting for potential confounders (using enter method). A p value < 0.2 was used first to identify the confounder variables and subsequently enter the variables into the analysis. Data analysis was conducted utilizing the SPSS (version 18.0) statistical software (SPSS Inc., Chicago, IL). A p value ≤ 0.05 was considered statistically significant.

**Results**

The demographic and clinical characteristics of the patients are summarized in Table 1. The mean width of the QRS was 146.54 ± 34.62 ms for all the patients, and 76.9% of the patients had surface electrocardiography evidence of a prolonged QRS complex (≥ 120 ms). The degree of MR ranged widely: 130 (51.8%) patients had ≤ mild MR and 121 (48.2%) had ≥ moderate MR. These two groups were compared in the further analysis. The etiology of the LV dysfunction was ischemic in 108 (43%) patients and idiopathic in 143 (57%) patients. This difference was not significant.

According to Table 1, the patients with significant MR were younger than the other group, although the difference was non-significant. The LVEF was significantly lower in the patients with significant MR than in those with no MR or mild MR. The LV systolic and diastolic dimensions and volume and the LV WMSI were higher in the patients with significant MR.

For the calculation of the dyssynchrony indices, a total of 3012 segments (12 segments per patient) were evaluated. Time-to-peak systolic velocity was not measurable in

| Patient characteristics | ≤ Mild MR     | ≥ Moderate MR | P value |
|-------------------------|---------------|---------------|---------|
| Age (y)                 | 55.38±15.19   | 51.63±17.94   | 0.086   |
| Male sex                | 100 (76.9)    | 87 (71.9)     | 0.362   |
| Etiology of cardiomyopathy |              |               | 0.987   |
| Ischemic cardiomyopathy | 56 (43.1)     | 52 (43.0)     |         |
| Dilated cardiomyopathy  | 74 (56.9)     | 69 (57.0)     |         |
| Left ventricular ejection fraction (%) | 23.28±7.40     | 19.83±6.13   | <0.001  |
| Left ventricular diastolic diameter (mm) | 61.86±6.98     | 68.70±8.73   | <0.001  |
| Left ventricular systolic diameter (mm) | 52.58±9.88     | 61.50±14.04  | <0.001  |
| Left ventricular end-diastolic volume (mm³) | 156.08±63.53  | 196.20±75.59 | <0.001  |
| Left ventricular end-systolic volume (mm³) | 118.91±60.84  | 156.29±73.11 | <0.001  |
| Wall motion score index  | 2.03±0.27     | 2.13±0.23     | 0.005   |

*Data are presented as mean±SD or n (%) MR, Mitral regurgitation
eight segments (one in each anterior, inferior, and posterior basal segment; one in each anterior, inferior, and posterior segment; and two in the anteroseptal basal segments). In Table 2, the dyssynchrony indices are compared between the patients with and without significant MR. According to Table 2, no differences were observed in the mean value of the various dyssynchrony parameters between the two groups. The difference of the mean QRS duration, IVMD, and Ts-basal-SD were in the significant level and needed further adjustment to determine any independent effect of these parameters on the severity of MR.

Using multivariate analysis the relationships between the MR severity and the QRS duration and the dyssynchrony indices, including IVMD and Ts-basal-SD, were adjusted for potential confounders (age, WMSI, and LV end-systolic volume). After adjustment, there was no significant impact of the QRS, IVMD, and Ts-basal-SD on the severity of MR (Table 3).

### Discussion

This study demonstrates that the severity of MR was not correlated with the QRS duration, the intra- and interventricular dyssynchrony indices by echocardiography in the patients with ischemic or dilated cardiomyopathy.

It has been described that intraventricular mechanical dyssynchrony is an important contributor to functional MR. Findings by previous studies are controversial in this regard. Soyama et al. studied 32 patients with dilated cardiomyopathy and found no significant correlation between dyssynchrony and MR severity. However, a recent study by Sardari et al. reported a significant association between dyssynchrony and MR severity.

**Table 2. Comparison of dyssynchrony markers between the study groups**

|                        | ≤ Mild MR (n=130) | ≥ Moderate MR (n=121) | P value |
|------------------------|-------------------|-----------------------|---------|
| **QRS duration**       | 150.75±34.66      | 142.03±34.03          | 0.050   |
| Aortic pre-ejection time| 130.88±43.35      | 126.77±29.04          | 0.375   |
| Pulmonary pre-ejection time | 92.20±33.05 | 94.09±22.68          | 0.595   |
| Interventricular mechanical delay | 41.60±29.50 | 35.00±22.01          | 0.045   |
| Ts-all-delay           | 119.73±55.59      | 112.83±44.31          | 0.276   |
| Ts-all-SD              | 42.15±19.35       | 38.71±15.24           | 0.118   |
| Ts-basal-delay         | 107.04±55.37      | 96.72±43.20           | 0.100   |
| Ts-basal-SD            | 42.56±21.60       | 37.79±17.34           | 0.056   |
| Basal-septal-lateral delay | 58.62±40.27  | 50.99±34.72           | 0.111   |
| Mid-septal-lateral delay | 60.50±36.60  | 55.53±36.46           | 0.282   |
| Basal-anteroseptal-posterior delay | 67.81±42.18 | 53.73±40.27          | 0.501   |
| Mid-anteroseptal-posterior delay | 55.97±41.96 | 52.35±43.01          | 0.506   |
| Mid-anterior-inferior delay | 68.01±48.27 | 59.81±38.75          | 0.142   |
| Basal-septal-posterior delay | 56.58±49.25  | 50.45±39.21           | 0.279   |
| Mid-septal-posterior delay | 57.81±42.18  | 53.73±40.27           | 0.435   |
| Ts-eight segments delay | 100.04±50.38  | 99.77±46.61           | 0.965   |
| Ts-eight segments SD   | 39.33±21.15       | 38.35±17.65           | 0.691   |

*All variables are presented as mean±SD in "milliseconds"

Ts, Time-to-peak systolic velocity; SD, Standard deviation

**Table 3. Effect of unadjusted and adjusted association between QRS and dyssynchrony indices and severity of mitral regurgitation in cardiomyopathy patients (n=251)**

|                        | OR     | 95% CI          | P value |
|------------------------|--------|-----------------|---------|
| **QRS duration**       |        |                 |         |
| Unadjusted             | 0.993  | 0.985-1.000     | 0.051   |
| Adjusted               | 0.993  | 0.986-1.002     | 0.126   |
| Interventricular mechanical delay |        |                 |         |
| Unadjusted             | 0.990  | 0.981-1.000     | 0.049   |
| Adjusted               | 0.993  | 0.982-1.005     | 0.251   |
| Ts-basal-SD            |        |                 |         |
| Unadjusted             | 0.987  | 0.974-1.001     | 0.056   |
| Adjusted               | 0.988  | 0.973-1.004     | 0.145   |

* Adjustments were performed for age, wall motion score index, and left ventricular end-systolic volume.

Ts, Time-to-peak systolic velocity; SD, Standard deviation
cardiomyopathy and showed that the presence of functional MR correlated with a significant delay in mechanical activity between the LV segments supporting the lateral and medial papillary muscles, as assessed by the difference in the time-to-peak systolic myocardial strain. Agricola et al. showed that the degree of MR was associated mainly with the mitral deformation indices and reported that the regional dyssynchrony also had an independent association with the degree of MR, with a minor influence in patients with DCM but not in those with ICM, which is in line with the present study. They also found that the QRS duration had no effect on the severity of functional MR. In the most recent study, Liang et al. demonstrated that in patients with LV systolic dysfunction, significant functional MR was determined not only by the mitral valve tenting area, but also by the degree of the global LV systolic dyssynchrony. The difference between the studies is possibly due to the difference in the definition of LV dyssynchrony. LV dyssynchrony was defined as the difference in the time-to-peak systolic myocardial strain by Soyama et al. and as the SD of time-to-peak systolic velocity of 8 (not 12) LV segments by Agricola et al. Elsewhere, Liang et al. defined dyssynchrony as delay of time-to-peak systolic velocity of twelve LV segments (one of the dyssynchrony indices in our study). Finally, our study demonstrated that none of the previously defined dyssynchrony indices were associated with the degree of MR. In addition, the results of the Donal et al. study, using regional strain analysis in 87 patients with DCM, demonstrated that the degree of functional MR was determined not only by the mitral orifice characteristics but also by the LV characteristics, especially longitudinal contractility (strain of LV mid-lateral wall) and dyssynchrony defined as the time delay between the septal and lateral mid-portion strain divided by RR squared root. In line with our study, the authors found that MR was not correlated with interventricular mechanical delay and pre-ejection period of the aortic valve.

In the present study, the patients with a higher degree of functional MR had a greater LV diameter and volumes, which chimes in with a previous description that in patients of functional MR had a greater LV diameter and volumes, ejection period of the aortic valve. Correlated with interventricular mechanical delay and pre-ejection period of the aortic valve.

Conclusions

In the light of the results of the present study, the degree of functional MR, adjusted for the LV regional and global remodeling indices, is not associated with the QRS duration and inter- and intraventricular dyssynchrony indices in patients with ICM or DCM. The impact of the etiology of cardiomyopathy on the severity of MR was not significant.

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