Assessment of Mechanical and Electrical Dyssynchrony in Cardiomyopathy.


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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) had shown great promise in improving hospitalization and mortality of the patients suffering from refractory heart failure (HF) inspite of optimal medical management. The goal of CRT is to reduce cardiac mechanical dyssynchrony, thereby enabling the heart to contract more efficiently. Mechanical ventricular dyssynchrony as estimated by electrical dyssynchrony, is assessed with the QRS duration. But electrical and mechanical dyssynchrony are not well correlated in all HF patients. The dyssynchrony might have been related to the underlying etiology of HF.

Objective: To compare the concordance of mechanical and electrical dyssynchrony in both ischemic and nonischemic cardiomyopathy patients.

Methods: Doppler echocardiography and strain echocardiography was performed in 76 patients presenting with heart failure due to ischemic cardiomyopathy (n=40) or nonischemic cardiomyopathy (n=36) with left ventricular ejection fraction <35% & New York Heart Association class III–IV, regardless of their QRS duration. Interventricular dyssynchrony was assessed by the time interval between preaortic and pre-pulmonary ejection times. Intra-ventricular dyssynchrony was assessed by using conventional Doppler and strain echocardiography. Obtained from the three standard apical view (TMinMax) and (2) the standard deviation of the averaged time-to-peak strain (TPS-SD, ms) and (3) time to peak myocardial systolic velocity (Ts-SD) of same segments.

Result: The correlation coefficient between QRS duration and mechanical interventricular dyssynchrony was significant (r=0.57, P=0.001) in patients with non-ischemic cardiomyopathy and insignificant (r=0.175, p=0.281) in patients with ischemic cardiomyopathy. The correlation coefficient between QRS duration and mechanical intra-ventricular dyssynchrony was significant in patients with nonischemic cardiomyopathy and insignificant (r=0.175, p=0.281) in patients with ischemic cardiomyopathy. The correlation coefficient between QRS duration and mechanical intra-ventricular dyssynchrony was significant in patients with nonischemic cardiomyopathy (r= 0.69, P = 0.001 for TMinMax; r=0.57, P = 0.001 for TPS-SD; r=0.48, p=0.003 for TS-SD) and insignificant in patients with ischemic cardiomyopathy (r=0.153; r=0.345 for TMinMax; r=0.178; p=0.273 for TPS-SD r=0.139; p=0.392 for TS-SD). Conclusion: This study showed that the relationship between electrical and mechanical dyssynchrony is dependent on the underlying etiology of heart failure.

Keywords: Cardiac resynchronization therapy, Cardiomyopathy, echocardiography.

INTRODUCTION

Throughout the past 20 years, we can see that Cardiac resynchronization therapy (CRT) is a clinically and cost-effective treatment for patients with both advanced and mild HF and a wide (intrinsic or paced) QRS complex. Efficacy of CRT was evaluated in various studies.

In the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study , the first double-blind CRT trial showed improvement of walking distance, quality of life, exercise capacity, left ventricular ejection fraction (LVEF) and peak VO2, paralleling LV reverse remodeling at 6 month after post CRT implantation (Abraham et al. 2002). [1]

Eligibility for CRT is traditionally based on New York Heart Association (NYHA) Functional Classification of symptoms, the ACC/AHA (American College of Cardiology/American Heart Association) stages of heart failure, rhythm, QRS duration, left ventricular ejection fraction (LVEF) (Epstein et al. 2008; Stevenson et al. 2012 and
Dickstein et al. 2010).\(^{[2-4]}\)

The quantification of LV dysfunction is a cornerstone for determining candidacy for CRT. An LVEF of <35% is the most common criterion for candidacy of CRT. In the current guidelines QRS duration >120 ms is the electrical criteria used to determine eligibility for CRT in NYHA class III-IV patients with sinus rhythm (Tang et al. 2010; Rickard et al. 2011).\(^{[5,6]}\)

The goal of cardiac resynchronization therapy (CRT) is to reduce cardiac mechanical dyssynchrony, thereby enabling the heart to contract more efficiently, increase LV ejection fraction and cardiac output, but with less work and lower oxygen consumption (Nelson et al. 2000).\(^{[7]}\)

However, while patients with either ischemic or nonischemic cardiomyopathy might benefit from CRT, up to 30% do not respond (Kass et al, 2003).\(^{[8]}\)

The data indicate that on a population basis non-response is multi-factorial and the extent of mechanical dyssynchrony, left ventricular pacing site and cause of congestive heart failure are likely to be important (Birnie et al, 2003).\(^{[9]}\)

QRS duration >120 ms is the electrical criteria used to determine eligibility for CRT in NYHA class III-IV patients with sinus rhythm (Tang et al. 2010; Rickard et al. 2011).\(^{[5,6]}\)

Echocardiography

Standard four-window trans-thoracic echocardiography was performed using a Vivid 7 (General Electric, Milwaukee, WI, USA) equipped with a variable frequency phased-array transducer (2.5–3.5–4.0 MHz). The echocardiographic measurement of left ventricular end diastolic diameter by M-mode and LVEF was measured from two-dimensional images by using Simpson’s biplane method in accordance with the recommendation of the American Society of Echocardiography. Pulsed Doppler was used to record right and left ventricular outflow tract ejection flows. The apical four-chamber, two chamber and long axis view in color-tissue Doppler was imaged and stored on a magneto-optical disk for further analysis. ECG was adjusted to be noise free with a delineated QRS waveform. Position the LV cavity in the center of the sector and aligned as vertically as possible, to allow for the optimal Doppler angle of incidence with LV longitudinal motion. Regions of interest (a minimum of 5 - 10 mm to 7 - 15 mm) in the basal and mid region of opposing LV walls (4 regions/view) to determine time-velocity plot. The image sector was approximately 30°, as narrow as possible to maximize the frame rate (>140 frames/second). However, in patients with the largest ventricles, it was not possible to reach 140 frames/second with a view of the whole heart. In these extreme cases, each wall was scanned independently with an image sector adjusted for a frame rate range from 140 to 200 frames/second. The upper limit of 200 frames/second was determined to keep a narrow range of frame rates among the patients of the study. In this study, post systolic shortening (positive myocardial velocity after aortic valve closure, which may be greater than the ejection peak) was included as some previous studies have included in their dyssynchrony analysis. (Notabartolo et al. 2004).

All echo-Doppler and tissue Doppler measurements were analyzed by the average of five cardiac cycles, to minimize difference during the breath cycle.

Assessment of Dyssynchrony

Electrical dyssynchrony: Electrical dyssynchrony was ascertained by the width of the widest QRS complex, measured for each patient on a surface electrocardiographic recording, and considered as the electrical dyssynchrony value. In the present

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study QRS duration is measured from the beginning of the Q wave to the end of the S wave (Mohit et al. 2013)

**Mechanical dyssynchrony**

Mechanical dyssynchrony was estimated using Doppler echocardiography.

**Interventricular dyssynchrony:**

Interventricular dyssynchrony was ascertained by the time interval between the preaortic and pre-pulmonary ejection times. The aortic pre-ejection time was measured from the beginning of QRS complex to the beginning of the aortic flow velocity curve recorded by pulsed wave (PW) Doppler in apical 5-chamber view. The pulmonary pre-ejection time was measured from the beginning of 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 determines the interventricular mechanical dyssynchrony (IVMD) and delay> 40 ms indicates significant interventricular dyssynchrony and was demonstrated to predict response to CRT (Cleland et. al 2005).

**Intraventricular dyssynchrony:**

Intraventricular dyssynchrony was assessed by using Doppler echocardiography and based on three indices:

1. The time delay between the earliest and the latest peak values of negative strain (active deformation) recorded in the basal and mid segments of 6 left ventricular wall (lateral, septal, anterior, inferior, anteroseptal and posterior) walls in the apical four-chamber, two chamber apical and apical three chamber view (TMinMax)
2. The standard deviation of the averaged time-to-peak strain (TPS-SD, ms) and time to peak myocardial systolic velocity (Ts-SD) of 12 middle and basal LV segments were obtained from the three standard apical views.

For each studied segment of TDI derived strain analysis, the time interval was determined from the beginning of the QRS complex to the peak negative value of strain within the analyzed cardiac cycle. To overcome even slight differences in heart rate, all temporal parameters were normalized by dividing by the square root of the cycle length.

TSI is a parametric imaging tool derived from two-dimensional tissue Doppler images. It automatically calculates Ts in every position in the image with reference to the QRS interval. The TSI algorithm detects positive velocity peaks within a specified time interval, and the color coding ranges from green (earliest-20-150 ms), yellow (150-300 ms), red (latest-300-500 ms) within this interval (Knebel et al. 2004) Using the user-defined event-timing tool, time from onset of the QRS complex to the aortic valve opening and closure was first measured in a separately recorded pulsed Doppler spectrum. To prevent the TSI system of measuring peak systolic velocities outside the ejection phase, the event-timing tool was used to manually adjust start and end times of the TSI. The start time was set at aortic valve opening and the end time at aortic valve closure. The automatic Ts detection, which is the basis for TSI, was performed within this time period. A quantitative measurement tool allows calculation of the median Ts within a 6 mm sample volume manually positioned within the two-dimensional TSI image. The sample volume was placed at the basal and mid of 6 LV wall and LV dyssynchrony was calculated automatically by the TSI software.

**Statistical Analysis**

Statistical analyses were performed using Stat view 20 (SAS Inc., Cary, NC, USA). Continuous parameters were expressed as mean±SD. Comparisons between groups (continuous parameters) were done by unpaired t test. Categorical parameters were compared by Chi-square test. Correlation analyses had done by Pearson R-coefficient value calculation, completed by a univariate linear regression analysis when the R-value was near 1. A p-value of <0.05 was considered significant.

**RESULTS**

A total of 76 patients with heart failure included in this study were divided into two groups, 40 patients in ischemic group and 36 patients in non ischemic group. The results of the study derived from data analyses are presented below.

**Comparison of functional class of HF between two groups**

More than half of the patients had NYHA IV in ischemic and non ischemic group. The mean NYHA was found 3.5±0.5 grade in ischemic group and 3.6±0.5 grade in non ischemic group. The mean difference was not statistically significant (p>0.05) between two groups.

| Table I: Comparison of functional class of HF between two groups (n=76) |
|---------------------------------|------------------|------------------|---------------|
|                                | Ischemic (n=40) | Non ischemic (n=36) | P-value |
| NYHA                           | n     | %       | n     | %       |               |
| I                              | 19    | 47.5    | 15    | 41.7    | ns            |
| IV                             | 21    | 52.5    | 21    | 58.3    |               |
| Mean±SD                        | 3.5±0.5| 3.6±0.5| 0.386* |
| Range (min-max)                | 3-4   | 3-4     |       |

Data are presented as mean±SD. Unpaired t-test was used to compare functional class of HF between two groups. p value <0.05 was considered as significant.

HF=Heart failure. N=Number of study population. NS=Not significant. SD=Standard deviation.
Comparison of the Electrical dyssynchrony (QRS duration) between two groups

Table II shows electrical dyssynchrony (QRS duration) of the patients. It was observed majority of the patients had QRS duration <120 msec in ischemic group and majority of the patients had QRS duration ≥120 msec in non ischemic group. The mean QRS duration difference was not statistically significant (p>0.05) between two groups.

Table II: Comparison of the Electrical dyssynchrony (QRS duration) between two groups (n=76)

<table>
<thead>
<tr>
<th>Electrical dyssynchrony (QRS duration) (msec)</th>
<th>Ischemic (n=40)</th>
<th>Non ischemic (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>22 55.0</td>
<td>15 41.7</td>
<td></td>
</tr>
<tr>
<td>≥120</td>
<td>18 45.0</td>
<td>21 58.3</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>118.4 ±27.9</td>
<td>116.0 ±28.3</td>
<td></td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>70 -170</td>
<td>80 -150</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. Unpaired t-test was used to compare Electrical dyssynchrony (QRS duration) between two groups. p value <0.05 was considered as significant.

Comparison of mechanical intraventricular dyssynchrony (IVMD) between two groups

Table III shows mechanical intraventricular dyssynchrony (IVMD) of the patients. It was observed that almost two third (65.0%) patients had mechanical Interventricular dyssynchrony <40 msec in ischemic group and 27(75.0%) in non ischemic group. The mean mechanical Interventricular dyssynchrony was not statistically significant (p>0.05) between two groups.

Table III: Comparison of the mechanical intraventricular dyssynchrony (IVMD) between two groups (n=76)

<table>
<thead>
<tr>
<th>Mechanical intraventricular dyssynchrony (msec)</th>
<th>Ischemic (n=40)</th>
<th>Non ischemic (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>26 65.0</td>
<td>27 75.0</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>14 35.0</td>
<td>9 25.0</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>35.0 ±12.4</td>
<td>30.0 ±14.7</td>
<td></td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>5 -73</td>
<td>6 -67</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. Unpaired t-test was used to compare Mechanical intraventricular dyssynchrony (IVMD) between two groups. p value <0.05 was considered as significant.

Comparison of mechanical intraventricular dyssynchrony between two groups

Table IV shows mechanical intraventricular dyssynchrony of the patients. It was observed that majority of the patients had TPS-SD >60 msec in ischemic group and majority of the patients had TPS-SD ≤60 msec in non ischemic group. The mean TPS-SD was found higher in ischemic group than non ischemic group. The mean TPS-SD was statistically significant (p<0.05) between two groups. More than two third of the patients had TS-SD >34 msec in ischemic group and more than half of the patients had TS-SD >34 msec in non-ischemic group. The mean TS-SD was not statistically significant (p<0.05) between two groups.

Table IV: Comparison of mechanical intraventricular dyssynchrony between two groups (n=76)

<table>
<thead>
<tr>
<th>Mechanical intraventricular dyssynchrony</th>
<th>Ischemic (n=40)</th>
<th>Non ischemic (n=36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPS-SD (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>12 30.0</td>
<td>21 58.3</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>28 70.0</td>
<td>15 41.7</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>68.5 ±19.8</td>
<td>54.6 ±15.0</td>
<td></td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>32 -141</td>
<td>28 -98</td>
<td></td>
</tr>
<tr>
<td>TS-SD (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤34</td>
<td>13 32.5</td>
<td>17 47.2</td>
<td></td>
</tr>
<tr>
<td>&gt;34</td>
<td>27 67.5</td>
<td>19 52.8</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>40.5 ±12.5</td>
<td>39.7 ±16.9</td>
<td></td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>19 -71</td>
<td>18 -99</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. Unpaired t-test was used to compare Mechanical intraventricular dyssynchrony between two groups. p value <0.05 was considered as significant.

Correlation between electrical dyssynchrony (QRS duration) with mechanical inter-ventricular dyssynchrony (IVMD) in ischemic and non ischemic group (n=76)

Figure 1: Correlation between QRS duration with IVMD of ischemic patients

r = correlation coefficient
IVMD-Mechanical Interventricular dyssynchrony
N=Number of study population
The age of the patient population in our study was almost similar to those study done in Bangladesh earlier (Rahman et al. 2014; Yaakob et al. 2009). The authors found no significant association between ischemic and non ischemic group with LVId, LVEF and NYHA. A number of investigators Yaakob et al. (2009), Sutton et al. (2006), Bader et al. (2004) and Felker et al. (2002) also found similar findings in their respective studies. In this series it was observed that the presence of electrical dyssynchrony was little higher than previous study (Kashani and Barold 2005). This difference in finding may be due to the advanced heart failure. In the study population, the mean electrical dyssynchrony QRS duration was almost similar between two groups in this study and no statistical significant (p>0.05) difference was observed between two groups in this study and no statistical significant (p>0.05) difference was observed between two groups. Sutton et al. (2006) showed that the mean electrical dyssynchrony QRS duration was alike between two groups. This finding is similar to present study. The mean mechanical interventricular dyssynchrony in our study was 35.0±12.4 msec in ischemic group and 30.0±14.7 msec in non-ischemic group. Tournoux et al. (2007) in their study found that the type of underlying etiology of cardiomyopathy influences the degree of benefit conferred by CRT. In a subgroup study done by Sutton et al. (2006) showed that the mean decrease in LV volumes at 6 months was significantly less among patients with ischemic than among patients with non-ischemic cardiomyopathy. Zwanenburg et al. (2005) showed that the propagation of onset of myocardial shortening was consistently from septum to lateral wall in non-ischemic patients, versus no consistent direction of propagation in ischemic hearts. Non-ischemic cardiomyopathy generally affects the entire myocardium, and the QRS prolongation reflects the extent of fibrosis rather than specific abnormalities of impulse propagation (Kashani and Barold, 2005). In end-stage heart failure, fibrosis becomes more diffuse and homogeneous, probably explaining the higher correlation between mechanical dyssynchrony and QRS duration (Tournoux et al. 2007). In contrast, a large proportion of the myocardium may be unaffected in patients with ischemic cardiomyopathy despite a wide QRS complex and selective ischemic injury to the specialized conduction system can prolong the QRS complex in the absence of diffuse fibrosis. In ischemic group Tournoux et al. (2007) showed...
the relationship between electrical and mechanical dyssynchrony was insignificant. More heterogeneous scar in ischemic cardiomyopathy (Bleeker et al. 2006) may result in various patterns of myocardial activation, even among the patients with the greatest degree of remodeling. While electrical dyssynchrony can be estimated using various invasive (Auricchio et al. 2004) or noninvasive techniques (Jia et al. 2006 and Rudy 2006). QRS duration remains the simplest parameter available to measure electrical dyssynchrony. However, despite its widespread use in clinical practice, QRS duration may not accurately reflect electrical dyssynchrony because it may exclude abnormal late activation (small fragmented portions of the QRS complex may not be considered in the measurement of the QRS duration). In addition, the ischemic patients were significantly older and, if some of them had a brief history of cardiovascular events with heterogeneous disease, others may have had a longer history of HF with more global LV remodeling. Finally, the Doppler echocardiography method used in this study examined myocardial strain along with velocity as opposed to earlier studies looking at only myocardial velocity or displacement. Tournoux et al. (2007) looked at the true deformation of the two LV walls, but may have not fully represented the total LV mechanical dyssynchrony because there may be heterogeneous myocardial deformation, especially in ischemic cardiomyopathy.

The data of Fauchier et al. (2002) study nicely showed that the presence of mechanical intraventricular dyssynchrony is an independent factor of worsening HF and mortality and it was inconsistent with ischemic group. Similarly, in ischemic patients it was observed in this present series that QRS duration had insignificant correlation with mechanical interventricular dyssynchrony, TPS-SD, TS-SD and TMinMax. Similarly, Tournoux et al. (2007) found the relationship between electrical and mechanical dyssynchrony was insignificant for interventricular dyssynchrony as well as intraventricular dyssynchrony in ischemic patient. Similarly, Yaakob et al. (2009) found there was no significant correlation between QRS duration and the Ts-SD-12 in ischemic patient. No correlation between dyssynchrony and QRS width was seen in the heart failure patients observed by Knebel et al. (2004). The above study findings are closely resembled with the present study.

Leyya et al (2012) in their study showed that the non-ischemic heart failure etiologies are associated with better CRT outcomes. So, concordance of mechanical and electrical dyssynchrony is more likely to present in nonischemic patient. The similar study done by Donal et al. (2007) showed that the correlation between electrical and mechanical indices in patients with ischemic versus non-ischemic was dissimilar illustrating the importance of the assessment of mechanical dyssynchrony in these patients.

CONCLUSION

Our result suggested that there was concordance of mechanical and electrical dyssynchrony in nonischemic cardiomyopathy patients but there was discordance of mechanical and electrical dyssynchrony in ischemic cardiomyopathy patients. This study showed that the relationship between electrical and mechanical dyssynchrony is dependent on the underlying etiology of heart failure.

In future, a combined approach incorporating electrical and mechanical dyssynchrony indices can reduce number of non-responder of CRT in ischemic cardiomyopathy patients.

Example of Concordance and Discordance of electrical and mechanical dyssynchrony in nonischemic and ischemic cardiomyopathy patient respectively

Figure 3: A-48-years old male nonischemic cardiomyopathy patient with QRS duration 100 ms but no mechanical dyssynchrony between anteroseptal and posterior wall in apical long axis view

Figure 4: A-47-years old male nonischemic cardiomyopathy patient with QRS duration 140 ms and significant mechanical dyssynchrony between all segment stdev (41ms) demonstrated by TSI.
REFERENCES


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