Cardiac Resynchronization Therapy: Improving Patient Selection and Outcomes

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KEYWORDS. cardiac resynchronization therapy, systolic dyssynchrony index, three-dimensional echocardiography.

Introduction
Cardiac resynchronization therapy (CRT) can improve clinical outcomes in patients who have moderate to severe heart failure in the presence of an intraventricular conduction delay. In addition to standard pharmacologic therapy in patients with heart failure and dyssynchrony, CRT has shown to improve quality of life, heart failure symptoms, exercise capacity, and mortality. However, despite the benefits associated with CRT, approximately one-third of patients fail to respond to this therapy (i.e. display no improvement of symptoms) by the standard patient selection guidelines. CRT implantations can be associated with rare but potentially serious complications, including coronary sinus dissection and death. Additionally, significant costs associated with unnecessary CRT implantations are of great concern in the current climate of global economic pressures. Therefore, patient selection to decrease unnecessary implantations has become an important strategy to save health-care costs.

The systolic dyssynchrony index (SDI), a parameter derived from three-dimensional echocardiography (3DE), is useful in assessing global left ventricular systolic dyssynchrony, and may be one additional parameter utilized to help predict response to CRT. SDI is defined as the standard deviation of time to minimum systolic volume of the 16 left ventricular segments and expressed as a percentage of the R-to-R duration from the electrocardiogram. SDI values are obtained semi-automatically with less operator dependency, and may provide information useful in selecting candidates for CRT therapy.

Objective
The objective of this observational study is to determine if using an SDI greater than 5 would result in a high response rate to CRT (>15% reduction in left ventricular end systolic volume (LVESV) post-procedure follow-up). Additionally, will post-procedure optimization utilizing Doppler echocardiography, confirmed by 3DE, result in an even greater improvement of measures of hemodynamic parameters post procedure.

Methods
Utilizing SDI, a single-physician cardiology practice conducted a retrospective analysis of 12 consecutive subjects who had 3DE prior to CRT and who had post-procedure optimization. The following criteria were utilized as inclusion criteria for analysis: New York Heart Failure class II or III; left ventricular ejection fraction ≥35%; QRS interval >120 ms (one patient had a QRS interval of 104 ms but demonstrated severe dyssynchrony with an echocardiogram); SDI >5% by 3DE and; contractile lateral wall by 3DE. We utilized data from Kapetanakis and colleagues, who assessed patients having no cardiovascular disease and determined the average SDI to be 3.5 ± 1.8%. For those with cardiovascular disease and normal left ventricular ejection fraction, the mean SDI was 4.5 ± 2.4%. For mild, moderate, and
severe systolic dysfunction, the mean SDIs were 5.4 ± 0.8%, 10.0 ± 2%, and 15.6 ± 1%, respectively. Subject characteristics are shown in Table 1. Utilizing Doppler echocardiography, post-procedure adjustments of atrio-ventricular (AV) delay and ventricular-to-ventricular (VV) interval were optimized to improve hemodynamic parameters. Biventricular pacemaker optimization in our laboratory is performed utilizing the aortic valve velocity time interval (VTI) as a surrogate for stroke volume. We verify aortic valve VTI at different AV intervals and then choose the best AV interval. Once this has been completed, we used the best left ventricular to right ventricular timing so to determine the best stroke volume. We compared and confirmed our results with the baseline 3DE and post-optimization 3DE. We feel this is a very easy and reproducible procedure for optimization.

Analysis

Descriptive statistics were used to obtain means on four hemodynamic parameters: ejection fraction, LVESV, stroke volume, and SDI. Additional analyses, utilizing the paired t-test, were run to determine significance and effect size on mean changes of these hemodynamic parameters.

Results

After implantation of a CRT device, our subjects had a reduction in their LVESV by a mean of 18.9%. An even greater improvement was seen after post-procedure optimization with a reduction of LVESV by a total of 30.2% (p ≤ 0.001). Additionally, the average left ventricular ejection fraction post procedure improved by 40%, and after optimization an overall improvement from pre-procedure was 63.6% (p ≤ 0.001). Stroke volume increased post procedure by 38.7% and after optimization from pre-procedure by 48% (p ≤ 0.001). Lastly, SDI decreased by 83.3% (p ≤ 0.001) from pre-procedure to post procedure after optimization (Table 2). Figures 1–3 show snapshots of the 3DE results pre-implant, post implant but prior to optimization, and post implant after optimization from one subject included in the analysis.

Discussion

Left ventricular (LV) dyssynchrony refers to a lack of synchronization or coordination between the intraventricular electrical activation and subsequent mechanical contraction. When this occurs it affects LV morphology and function leading to worsening of pre-existing heart failure. Currently, guidelines suggest that patients with drug refractory heart failure and a prolonged QRS complex are ideal candidates for CRT therapy; on the basis of these criteria, however, up to 40% of them fail to improve, mostly due to poor patient selection, improper lead placement, or lateral wall scar. In recent years, preliminary data from single-site studies indicate that two-dimensional echocardiography and tissue Doppler-derived parameters of LV dyssynchrony could be better predictors of CRT response than the current guideline of prolonged QRS complex. However, these theories were soon refuted when the PROSPECT Trial, a multicenter study of more than 4,000 patients, reported results indicating that no single echocardiographic measure of LV dyssynchrony showed more than a modest level of sensitivity or specificity. Therefore, standard echocardiographic measures could not be recommended as a tool to improve patient selection for CRT beyond current guidelines.

Table 1: Population demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>Male (%)</td>
<td>58</td>
</tr>
<tr>
<td>Race: White (%)</td>
<td>75</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>68</td>
</tr>
<tr>
<td>NYHAC-III (%)</td>
<td>75</td>
</tr>
<tr>
<td>QRS complex duration (mean ms)</td>
<td>152 ± 52</td>
</tr>
</tbody>
</table>

NYHAC-III: New York Heart Association Functional Class.

Table 2: Mean comparisons pre-procedure compared with post-procedure pre-optimization and post-procedure post optimization (n=12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (pre-procedure)</th>
<th>Post procedure</th>
<th>Mean change/</th>
<th>Mean change</th>
<th>Total mean change</th>
<th>Effect size</th>
<th>t (total change)</th>
<th>Standard deviation</th>
<th>p (total change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>29.8</td>
<td>41.8</td>
<td>11.9/40</td>
<td>48.8</td>
<td>7.0</td>
<td>19.0/63.6</td>
<td>.94</td>
<td>8.83</td>
<td>7.44</td>
</tr>
<tr>
<td>LVESV</td>
<td>80.2</td>
<td>65.1</td>
<td>15.2/18.9</td>
<td>56.0</td>
<td>9.1</td>
<td>24.2/30.2</td>
<td>.87</td>
<td>5.978</td>
<td>14.04</td>
</tr>
<tr>
<td>SDI</td>
<td>10.0</td>
<td>3.6</td>
<td>6.4/63.5</td>
<td>1.6</td>
<td>2.0</td>
<td>8.4/83.8</td>
<td>.94</td>
<td>8.842</td>
<td>3.30</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>34.1</td>
<td>47.3</td>
<td>13.2/38.7</td>
<td>50.4</td>
<td>3.2</td>
<td>16.4/48</td>
<td>.84</td>
<td>5.1</td>
<td>11.04</td>
</tr>
</tbody>
</table>

Opt: optimization; LVESV: left ventricular end systolic volume; SDI: systolic dyssynchrony index.
The more modern form of echocardiography, 3DE, to assess dyssynchrony for potential CRT patient selection remains controversial. A parameter obtained with 3DE, the SDI, provides a comprehensive assessment of the radial, circumferential, and longitudinal ventricular contraction, simultaneously from all myocardial segments. It is the most frequently used validated parameter for predicting response to CRT. Utilizing SDI has been shown to prevent the use of CRT in potential non-responders. In a meta-analysis of LV dyssynchrony assessment and prediction of response to CRT therapy, Kleijn and colleagues concluded that 3DE is reliable and may have an added value to the current selection criteria for accurate prediction of the CRT response. Predicting non-responders is important because CRT is expensive and invasive.

Though the exact reasons for non-response to CRT in appropriately-selected patients is unknown, some theories exist, such as inadequate lead placement, scar burden, and suboptimal device settings. Individualized post-procedure optimization to improve AV and VV intervals by echocardiographic Doppler and 3DE significantly improved hemodynamic parameters in our study. Recently, one other study of 25 subjects was found in the literature that optimized patients post procedure using both AV and VV intervals. Utilizing a standard protocol, this group demonstrated that integrating 3DE for optimizing AV and VV intervals significantly improved LV function in CRT subjects.

**Limitations**

This was not a randomized controlled study, but rather a retrospective observational study utilizing a small population from a single-physician practice. Optimization occurred at different time intervals postoperatively between subjects. This was affected by when patients came to the physician’s office for a follow-up visit, possibly affecting consistent response to optimization. Though none of our patients were non-responders, this should be verified in a larger controlled study. Additionally, we utilized an SDI of >5%; however, a lower SDI may prove to be as successful in those with dyssynchrony.

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**March 12, 2009 – Pre-Implant**

LVEF 36%: LVEDV 119 ml: LVESV 76 ml: SDI is 14.89%: SV 43ml

**Figure 1:** This is an example of one subject’s three-dimensional echocardiogram prior to cardiac resynchronization therapy. This patient suffered from heart failure and obvious dyssynchrony as evidenced by an systolic dyssynchrony index of 14.89%. LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; SDI: systolic dyssynchrony index; SV: stroke volume.
Future perspectives

Based upon our observation from this small retrospective study, we feel failure rates can be reduced by improving the selection criteria. A large randomized study to determine if selecting patients by standard electrocardiographic criteria only compared to 3DE obtained SDI should be performed for further evaluation. Optimizing patients utilizing a standardized protocol will most likely provide consistent and reliable results.

Many studies, including ours, have calculated the SDI in 16 segments, and have excluded the apical cap segment in their SDI calculations due to its minimal contribution to ejection. However, Tani and colleagues investigated LV regional motion in all 17 segments and found that systolic wall motion of the apical cap might significantly contribute to LV systolic function and its synchronicity. They concluded that the apical cap, or all 17 segments, should be included in the SDI calculation. More studies should investigate this theory.

Conclusion

In this small single-site study, we observed an overall improvement in patients undergoing CRT who were selected utilizing SDI criteria of >5 (mean was 10) in addition to standard guidelines. The SDI of post-procedure patients dropped to 3.6, and after optimization utilizing 3DE, the overall SDI was 1.6. We conclude that SDI may be used to help select patients to determine potential response to CRT therapy, and that optimizing their AV and VV intervals utilizing 3DE can significantly improve hemodynamic parameters even further.

Figure 2: This is the same subject 6 weeks after cardiac resynchronization therapy implant. This patient was studied with three-dimensional echocardiography showing a 10% increase in the ejection fraction and an improvement in the systolic dysynchrony index to normal at <1%. LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; SDI: systolic dyssynchrony index; SV: stroke volume.
April 24, 2009 Post implant – post optimization
LVEF 51.5%: LVEDV 146.9ml: LVESV 71.4ml: SDI 0.51%: SV 75.5

Figure 3: Subject after implant and after optimization. Ejection fraction improved by another 5% and the systolic dyssynchrony index decreased by another 38%. LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; SDI: systolic dyssynchrony index; SV: stroke volume.

References


