QRS Prolongation Following Cardiac Resynchronization: Incidence, Predictors, and Outcomes

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ABSTRACT. Background: Following cardiac resynchronization therapy (CRT), the paced QRS duration may be more prolonged than the preoperative QRS. The outcome for these patients with a +QRS duration is uncertain. Methods: Analysis of 100 consecutive patients with successful CRT implantation. Results: 37 patients had a +QRS duration. Compared with those with a −QRS duration, these had a shorter baseline QRS (150.1 versus 176 ms, p=0.001) and more often had either anterior/lateral (QRS $\geq$ 28.5 ms) or posterior vein (QRS $\geq$ 3 ms) left ventricular (LV) lead location. Of 22 patients who improved by two classes, the mean difference in QRS was $\sim$ 18.1 ms. Of the 35 whose functional class did not improve, the mean QRS difference was $+5.0$ ms. Of the eight who worsened, the mean difference was $+33$ ms. Transthoracic echocardiograms at 3–6 months showed that a −QRS duration was associated with a higher mean LV ejection fraction and smaller left ventricular end diastolic dimension. Conclusions: A +QRS duration is associated with a worse clinical outcome. These patients have poorer LV function and size. Measurement of the paced QRS at the time of implantation, focusing on obtaining a −QRS duration, may improve outcomes in patients undergoing CRT.

KEYWORDS. cardiac devices, cardiac resynchronization therapy, heart failure.

Introduction

Prolongation of the QRS complex on the surface electrocardiogram (ECG) is a practical surrogate of cardiac dyssynchrony in patients with systolic dysfunction. Cardiac resynchronization therapy (CRT) can shorten the QRS complex with improvement in cardiac function and heart failure symptoms.1–6 However, following CRT a number of patients have a postoperative paced QRS duration (pQRS) which is more prolonged than the preoperative ECG.7–9 This continued cardiac dyssynchrony may partially explain the failure to improve in up to 30% of patients who receive CRT.2,10 It remains unclear what factors are associated with a more prolonged QRS (+QRS duration) in patients undergoing CRT.

The purpose of this analysis is 1) to determine the frequency of a +QRS duration following CRT, 2) to identify factors associated with a +QRS duration, and 3) to determine if patients with continued cardiac dyssynchrony have a less favorable outcome.

Methods

One hundred consecutive patients who underwent successful initial implantation of a CRT device at the University of Missouri were included in this study. All patients had a preoperative ECG with QRS duration ≥120 ms, a left ventricular ejection fraction (LVEF) ≤35% determined by echocardiography, and New York Heart Association (NYHA) functional class II–IV symptoms. The QRS duration on the surface ECG performed immediately prior to implantation was measured and the QRS morphology (left bundle branch block (LBBB), right bundle branch block (RBBB), and Intra Ventricular conduction defects (IVCD)) was assessed. The immediate
postoperative ECG was used to confirm biventricular pacing and to assess the pQRS duration. Preoperative and 3–6-month postoperative variables including demographic information, New York Heart Association (NYHA) functional class, and echo-derived parameters were obtained by electronic medical record review. Functional class assessment, ECG interpretation including the presence of biventricular pacing and QRS duration, and echo data were all assessed by the follow-up physician without knowledge of the purpose of the study. QRS duration was measured manually and double checked with computer-derived readings. Intraoperative features including lead position (apical, mid, basal) and location of the coronary sinus vein used for implantation (posterior, posterior/lateral, lateral, anterior/lateral) were determined by analysis of the postoperative chest X-ray and the coronary sinus angiogram obtained during the procedure. The distance between the tips of the left ventricular (LV) and right ventricular (RV) leads was measured using the posterior–anterior (PA) chest X-ray post implant, and was also measured using software-provided calipers on the coronary sinus angiogram at the time of implantation. Percent pacing was assessed by device interrogation at the first postoperative visit. The study was approved by our Institutional Review Board.

Statistical analysis

Statistical analyses were performed using SAS v9 (SAS Institute Inc., Cary, NC). Summary statistics for continuous variables are presented as mean ± SD and categorical variables as proportions. Logistic regression analysis was performed to analyze the relation between the change in QRS duration post implantation and improvement assessed clinically by the change in NYHA class. Correlation analysis and linear regression were used to examine the relationship between change in QRS duration and LVEF and LV size determined by two-dimensional echocardiogram when available. Both Pearson and Spearman rank correlations were examined. Analysis of covariance was used to examine the relationship between change in QRS duration and coronary sinus lead position, determined by chest X-ray and coronary sinus angiogram review post implantation. The baseline QRS duration was used as a covariate. Multiple pairwise comparisons of positions were performed using the Tukey–Kramer adjustment. Statistical significance was set at p < 0.05.

Results

Baseline characteristics of the overall population stratified by QRS duration after device implantation are shown in Table 1. The study participants represent a typical CRT population with a mean age of 68.7 ± 10.7 years. Males constituted 69% of the population. The etiology of heart failure was ischemic in 70%. Preoperative ECG findings included a mean QRS duration of 165.5 ± 26.1 ms. The QRS morphology was LBBB in 63 patients, RBBB in 18 patients, and non-specific IVCD in 19 patients. Atrial fibrillation was present in 28% of the study population. The NYHA class at baseline was 3.0 ± 0.2, and the mean LVEF was 25.2 ± 7.3%.

Table 1: Baseline characteristics stratified by change in QRS duration after implantation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients n=100</th>
<th>More prolonged (+) QRS duration n=37</th>
<th>More narrow (-) QRS duration n=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>68.7 ± 10.7</td>
<td>70 ± 10.7</td>
<td>67.95 ± 10.6</td>
</tr>
<tr>
<td>Men</td>
<td>69</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>Cardiac risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (30%)</td>
<td>13 (35%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (75%)</td>
<td>27 (73%)</td>
<td>48 (76%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>64 (64%)</td>
<td>24 (65%)</td>
<td>40 (63%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>68 (68%)</td>
<td>25 (68%)</td>
<td>43 (68%)</td>
</tr>
<tr>
<td>% Etiology of heart failure (ischemic)</td>
<td>70 (70%)</td>
<td>25 (68%)</td>
<td>45 (71%)</td>
</tr>
<tr>
<td>NYHA class (mean)</td>
<td>3.0 ± 0.2</td>
<td>2.95 ± 0.2</td>
<td>3.1 ± 0.2</td>
</tr>
<tr>
<td>QRS morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td>63 (63%)</td>
<td>22 (60%)</td>
<td>41 (65%)</td>
</tr>
<tr>
<td>RBBB</td>
<td>18 (18%)</td>
<td>9 (24%)</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>IVCD</td>
<td>19 (19%)</td>
<td>6 (16%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>ECG rhythm (atrial fibrillation, %)</td>
<td>28 (28%)</td>
<td>9 (24%)</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>QRS duration pre-implant (ms)</td>
<td>166.15 ± 0.15</td>
<td>150.1 ± 20.4</td>
<td>175.7 ± 25.8*</td>
</tr>
</tbody>
</table>

* p < 0.001 compared to those with a more prolonged narrow QRS duration.

ECG: electrocardiogram; LBBB: (left bundle branch block; LVEF: left ventricular ejection fraction; LVEDd: left ventricular end diastolic dimension; RBBB: right bundle branch block.
fibrillation was present on the baseline ECG in 28 patients. The mean NYHA class was $3 \pm 0.2$, with 94 patients classified as NYHA class III. The mean LVEF was $25.2 \pm 7.3\%$. The mean LV end diastolic dimension was $5.9 \pm 0.9$ cm. Patients were prescribed recommended heart failure medications: 95% of patients received either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker, and 92% received $\beta$-blockers. The only significant difference between those patients with a more narrow QRS ($-\text{QRS duration}$) and those with a $+\text{QRS}$ duration was the baseline QRS duration.

The most common coronary sinus vein used for LV placement was the posterior lateral vein (52%) followed by the lateral vein (31%), anterior/lateral vein (10%), and posterior vein (7%). In the postoperative chest X-ray, the LV lead was in the mid-location in 44 patients, at the apex in 43 patients, and in a basal location in 13 patients. The RV lead was placed in the RV apex in 94 patients. The distance between the tips of the RV and LV lead during implantation (right anterior oblique projection) was $59.55 \pm 20.7$ mm and on postoperative PA chest X-ray was $56.4 \pm 19.4$ mm. The mean amount of biventricular pacing at the first postoperative visit was $98 \pm 2.4\%$. The mean postoperative pQRS duration was $161.4 \pm 25$ ms. Thirty-seven patients had a pQRS duration which was more prolonged than that at baseline and improvement in NYHA functional class was related to the difference between the preoperative and postoperative QRS duration. Of the 22 patients who improved by two functional classes, the mean change in QRS duration was $-18.1 \pm 26.25$ ms. Of the 35 patients who improved by one functional class, the mean change in QRS duration was $-14.7 \pm 23.35$ ms. Of the 35 patients who had no change in functional class the mean change in QRS duration was $+5.0 \pm 30.3$ ms. Of the eight patients who declined in functional class, the mean change in QRS duration was $+33.0 \pm 29.7$ ms. Differences among the four groups are significant at the $p<0.0001$ level (Figure 1).

In the 43 patients who showed no clinical improvement, the change in mean QRS duration was $+10.2 \pm 31.8$ ms. In the 57 patients who experienced clinical improvement, the change in mean QRS duration was $-16.0 \pm 24.3$ ms.

**Predictors of a $+\text{QRS}$ duration**

Patients who had the LV lead placed in the posterior, posterior lateral, or lateral coronary sinus vein had a difference between the pre- and postoperative pQRS duration of $+3$ ms $\pm 34.8$, $-6.6 \pm 29.8$ ms, and $-14.1 \pm 22.2$ ms respectively. Patients with the LV lead placed in the anterior/lateral coronary sinus vein had a difference between the pre- and postoperative QRS duration of $+28.5 \pm 34.4$ ms (Figure 2). Analysis of covariance showed a significant difference between the mean QRS duration in patients with an LV lead placed in the anterior/lateral or posterior location ($+\text{QRS}$ duration) compared with those with the LV lead placed in the posterior/lateral or lateral position ($-\text{QRS}$ duration) without significant change in NYHA class among the four positions. No significant relation of improvement in

![Figure 1](image-url): Comparison of the change between the preoperative QRS duration and the postoperative QRS duration with change in NYHA class. NYHA 0 indicates no change, a negative value indicates improvement and a positive value indicates deterioration. Differences among the four groups are significant at $p<0.0001$. 

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**The Journal of Innovations in Cardiac Rhythm Management, August 2013**
functional class or QRS duration could be established based upon distance between the tips of leads as measured on chest X-ray or distance between leads at the time of implantation. Apical, mid, or basal location did not influence the QRS duration and did not influence clinical outcomes.

Amount of QRS narrowing and clinical improvement

In order to visualize the relationship between change in QRS and improvement in NYHA class, the differences between the pre- and postoperative pQRS durations were divided into quintiles. Patients with even a slightly −QRS duration had a higher likelihood of improvement. Patients with a more prolonged QRS duration were less likely to improve (Figure 3). The likelihood of having a −QRS duration was related to the baseline QRS duration. In 20 patients with a preoperative QRS duration of 120–140 ms, only seven (35%) patients had a −QRS duration. Of the 19 patients with a preoperative QRS duration >190 ms, 17 (89%) had a −QRS duration (Figure 6). However, clinical improvement was related more to a reduction in QRS duration than the baseline QRS duration. If patients with a baseline QRS duration of 120–140 ms had a −QRS duration, the likelihood of clinical improvement was 71% compared with 38% in those with +QRS duration. In contrast, in patients with a baseline QRS duration of >190 ms, those with a −QRS duration had a likelihood of improvement of 82%. No improvement was seen in patients with a QRS duration >190 ms when the postoperative QRS duration was more prolonged.

ECHO parameters

Although a postoperative echocardiogram with measurements of LVEF and LV size at 3–6 months was available for only 43 and 24 patients, respectively, there was a relationship between the difference between the change in pre- and postoperative QRS duration and LVEF and LV size. Patients with a −QRS duration more likely had a higher LVEF; patients with a +QRS duration more likely had a lower LVEF (Spearman’s r = −0.424, p = 0.0046, Figure 4). Of the 25 patients who had a −QRS duration, the mean postoperative LVEF was 38.4 ± 13.4%, and for the 18 patients who had +QRS duration the mean postoperative LVEF was 26.8 ± 9.1. For every 10-ms reduction in QRS duration, the LVEF had an estimated increase of 1.37% (95% CI 0.42–2.32) based on fitting a linear regression model. Left ventricular end diastolic dimension (LVEDd) was available for only 24 patients postoperatively. Patients with a −QRS duration had a smaller LVEDd than patients with a +QRS duration. Of the 14 patients who had a −QRS duration, the mean LVEDd was 5.5 ± 0.9 cm. Of the 10 patients who had a +QRS duration, the mean LVED was 6.2 ± 1.1 cm (Figure 5). Statistical tests for differences were not performed due to the relatively small sample size.
Discussion

In this study, over one-third of patients following CRT implantation have a +QRS duration. Predictors of a +QRS duration include lead position in the coronary sinus, especially location in the posterior or anterior locations, but not the distance between LV and RV lead or apical location compared with mid- or basal locations. Patients with a +QRS duration have more functional impairment regardless of baseline QRS duration and had a lower LVEF and a larger LVEDd than patients with a -QRS duration.

Approximately 30–40% of the patients who undergo CRT do not improve. A variety of clinical, demographic, electrocardiographic, or procedural reasons for lack of improvement have been proposed, including the change in QRS duration. Lecoq classified patients as improved after CRT if they were alive, had not been rehospitalized for heart failure, had improvement in NYHA class, and had an increase in the peak VO₂ or 6-min walk test by >10%. The amount of QRS shortening after CRT predicted a positive response. In the PROSPECT-ECG substudy, the difference in QRS duration was a predictor of improvement in the clinical composite score. Iler et al. showed that there was increased mortality and more cardiac transplantation in patients with a wider post-implantation QRS. Rickard et al. demonstrated a deterioration of LV function with QRS prolongation induced by CRT. A small study by Stockburger noted that 11 of 21 patients with a LBBB had shortening of the QRS duration after a mean follow-up of 21 months. There was a trend toward smaller LV dimensions with shorter QRS duration but the results were not statistically significant. In contrast, in a study by Sweeney reverse remodeling did not correlate with changes in LV activation time but was more correlated with the absence of scar based on a QRS score. These data illustrate the complex nature of all the factors that contribute to improvement in LV size and function after CRT. The benefit of the current data is that QRS duration can be assessed during CRT implantation and that a goal of a more narrow QRS duration, indicating less cardiac dyssynchrony, may improve clinical outcomes. In a study of 202 patients, Sweeney et al. correlated the reverse remodeling after CRT to LV activation time compared with QRS duration, with which they showed a weak correlation. The measurement of ventricular activation sequence and ventricular fusion in this study is much more complex than measurement of QRS duration in our study, which can be done in a simple 12-lead ECG without any magnification and sophistication. Another possible reason for non-response to CRT could be the presence of transmural scar tissue in the posterolateral LV segments, suggesting that lead placement in scar region can cause QRS to be prolonged and should be avoided.

Figure 3: Histogram showing relation between change in QRS duration divided in quintiles and percentage of improved patients.
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**Figure 4**: Scatter diagram showing change in QRS duration and relation to change in left ventricular ejection fraction (LVEF). Quadrant A indicates improved LVEF with a $-\text{QRS}$ duration and Quadrant D indicates deteriorated LVEF with a $+\text{QRS}$ duration.

**Figure 5**: Scatter diagram showing change in QRS duration and its relationship to change in left ventricular end diastolic dimensions. Quadrant C indicates decreasing left ventricular (LV) size with a $-\text{QRS}$ duration and quadrant B indicates increasing LV size with a $+\text{QRS}$ duration.
The position of the coronary sinus lead and the distance between the tips of RV and LV leads has been thought to affect outcomes. Butter et al. 24 have shown a favorable outcome with a lateral lead position, and Gold et al. 25 postulated better hemodynamic response in patients with a lateral lead placement. An anterior lead placement has been considered to have a deleterious effect on outcomes. 26 The results of the current study show that a −QRS duration is more likely if the LV lead is in lateral and posterior–lateral position, and a +QRS duration is more likely from the anterior or posterior location. We could not establish any statistically significant correlation between distance between the LV and RV lead and either QRS duration or clinical outcomes. This contrasts to the study by Merchant et al., 27 who demonstrated a significant correlation between interlead distance and LV lead electrical delay and outcomes. Our study suggests that intraventricular conduction, as measured by the difference in the pre- and postoperative QRS duration, may be more important than the distance between the RV and the LV lead.

Most studies have stressed the importance of the preoperative QRS duration in predicting outcome. A meta-analysis of five major trials suggested that the benefit of CRT was evident only in patients with pre-implantation QRS of >150 ms. 28 Another meta-analysis concluded that there is no significant reduction in death and heart failure worsening in patients with a QRS duration <150 ms. 15 Similar results were shown in other clinical studies. 29–31 Beshai et al. 32 have reported no benefits of CRT in patients with narrow QRS complex. Similarly Kronborg et al. 32 found that patients who have QRS duration between 150 and 200 ms are the ones with most symptomatic improvement. However, Reynolds et al. 29 found no relationship between baseline QRS and clinical outcome when the QRS was more than 130 ms. One explanation for these differences may be that the change in QRS duration rather than the preoperative QRS duration may be a more important predictor of outcome.

Regardless of the preoperative QRS duration, these data suggest that measurement of the QRS duration at the time of implantation with an attempt to shorten the QRS duration should enhance the success of CRT. In one study a relationship was established between electrical delay defined by time interval from the first deflection on

![Figure 6: The percentage of patients with a more narrow QRS duration based on the preoperative QRS duration and the clinical response.](image-url)
a surface ECG to local intrinsic activation at the LV stimulation site (QLV) and reverse remodeling in patients with CRT, and it was postulated that measurement of QLV interval during the procedure and repositioning the LV lead based on the QLV interval could be associated with a better outcome. However, it needs manual measurement of the QLV interval compared with QRS duration, which is measured by machine. To maximize the benefits, both measurement of QLV and QRS can be combined. To our knowledge, Lecoq et al. have performed intraprocedural pace mapping to obtain the narrowest possible QRS duration during implant, but it is unclear whether this study utilized a 12-lead ECG or limb leads only to determine the QRS duration. Precordial leads are usually not used intraoperatively because of visual interference with lead placement, and in our experience measurement of the QRS duration with limb lead ECGs in the electrophysiology laboratory does not correlate well with a 12-lead-derived QRS duration. Studies have shown that QRS duration is wider in precordial leads than in limb leads, so the use of limb leads only for QRS measurement during implantation will need further study. There could be different approaches when a prolonged QRS duration is encountered: invasively, the LV lead or RV lead can be repositioned during the procedure; non-invasively, a multichannel LV lead can be used which allows programming of different vectors, or LV–RV timing can be programmed to obtain the narrowest QRS duration. Again, all these approaches are still investigational and need further studies before being implemented in practice. At our center, we usually program the LV to precede the RV activation by 20 ms, but we are finding that the QRS can be shortened by programming the RV before the LV. This involves performing a 12-lead ECG with each adjustment of the CRT device. With current technology, our proposal would require measurement of the QRS duration at baseline with a 12-lead ECG before implantation, connection of the CRT device for biventricular pacing with measurement of a 12-lead ECG during the implantation procedure, and then acquisition of another 12-lead ECG during biventricular pacing.

Limitations
This is a small retrospective study and subject to all the biases inherent in this type of analysis, including failure to measure important preoperative, operative, and postoperative variables. The reliance of NYHA clinical classification is subjective and subject to bias. The limited number of postoperative echocardiograms performed in the 3–6-month follow-up period limits our conclusions. Finally, the postoperative pQRS duration may be influenced by alternating of LV and RV timing. This was not systematically performed at implantation and may influence the postoperative pQRS duration.

Conclusions
Over one-third of patients have a +QRS duration after CRT. The difference between the pre- and postoperative QRS duration is a powerful predictor of clinical outcome in patients with CRT regardless of baseline QRS duration. A +QRS duration is usually achieved from the posterior–lateral and lateral position. Measurement of the QRS duration during implantation, with an emphasis on obtaining a +QRS duration, may improve clinical outcomes in patients with CRT.

References


