The role of interventricular conduction delay to predict clinical response with cardiac resynchronization therapy

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BACKGROUND Pacing at sites with late electrical activation or greater interventricular delay is associated with improvement in measures of cardiac resynchronization therapy (CRT) response, primarily reverse remodeling. However, little is known about whether such lead positions improve heart failure (HF) clinical outcomes.

OBJECTIVE The purpose of this study was to assess the association between interventricular electrical delay and HF clinical outcomes.

METHODS The Pacing Evaluation-Atrial Support Study was a multicenter randomized trial of patients undergoing CRT-defibrillator implantation. Interventricular delay was measured as the unpaced right ventricle-left ventricle (RV-LV) interval in sinus rhythm. The HF clinical composite score was the primary end point. In addition, the time to first HF hospitalization or death was measured and events were adjudicated by a blinded core laboratory. The cohort was divided at the median RV-LV interval into short (<67 ms) and long (≥67 ms) subgroups. In addition, receiver operating characteristic curves were constructed to identify the optimal cutoff of the RV-LV interval and spline analysis was performed to assess RV-LV interval as a continuous variable.

RESULTS A total of 1342 patients were included in this study. The clinical composite score at 1 year differed between groups, with more patients improving and fewer patients worsening in the long RV-LV group (P = .014). The time to first HF hospitalization or mortality also differed with a lower risk of an event in the long RV-LV group (hazard ratio 0.62; P = .002). Multivariate analysis showed that RV-LV time (hazard ratio 0.71; P = .038) and sex were independent predictors of this outcome.

CONCLUSION Baseline interventricular delay is a strong independent predictor of clinical response to CRT.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Interventricular delay; Pacing; Outcomes

Introduction

Cardiac resynchronization therapy (CRT) is an effective therapy for patients with heart failure (HF) with a reduced ejection fraction and QRS prolongation. Despite the well-documented benefits of CRT,1–5 a significant minority of patients are classified as nonresponders,6–8 so reducing the nonresponder rate is an important goal for future development.

Traditionally, left ventricular (LV) leads were placed preferentially on the lateral wall.9 However, post hoc analyses from several large pivotal clinical trials of CRT showed little effect of anatomic LV lead position on outcomes, with the exception of worse response in apical positions.10–12 In contrast, lead positions in areas of late electrical activation have been associated with a better predictive value for a variety of end points, such as acute hemodynamic response, reverse remodeling, and quality of life.13–19

Interventricular electrical delay is another measure of electrical dyssynchrony that reflects both right ventricular (RV) and LV conduction between the implanted leads. This measure is associated with remodeling responses to CRT.17–19 However, the predictive values of LV or interventricular electrical delays have not been assessed for clinical outcomes in multicenter clinical trials.

Methods

The present study is a post hoc analysis designed to evaluate the relationship between LV electrical delay, as assessed by the RV-LV duration, and outcomes in the Pacing Evaluation-Atrial Support Study (PEGASUS). The PEGASUS protocol was reviewed and approved by all participating institutional review boards or ethics committees, and all patients gave their written informed consent before CRT implantation. The details of the design and primary results of the PEGASUS have been published previously.20,21 Briefly, this was a multicenter randomized trial of atrial support pacing among patients with New York Heart Association (NYHA) class III or IV HF undergoing...
CRT-defibrillator implantation. The major inclusion criteria were LV ejection fraction (LVEF) ≤35% and QRS duration ≥120 ms. Patients were required to be in sinus rhythm, and those who had complete heart block were excluded. A total of 1433 patients were randomized at 141 centers into 3 arms to assess the atrial pacing effect on CRT. Since there were no differences in primary or secondary outcomes between these groups, data were pooled for the present analyses. The RV-LV interval was calculated by a validated device-based algorithm of the intracardiac electrograms. This was available at implantation for the 1342 randomized subjects (94%) and is the cohort included in this study.

CRT implantation was performed using standard techniques, with no requirements regarding lead positions. As per clinical standards at the time of enrollment, a vast majority of RV leads were placed at the apex. The final LV lead location as viewed in the left anterior oblique projection was classified by the investigator. The locations were grouped as either posterior/lateral or anterior/septal for analyses.

The primary end point of the PEGASUS was a clinical composite score consisting of all-cause mortality, HF events, NYHA functional class, and the patient portion of the global assessment tool. For the purpose of this trial, the 3 outcomes were defined as follows:

1. Worsened: The patient dies or has an HF event or exhibits moderately or markedly worse global assessment or worsening NYHA class.
2. Improved: The patient has not worsened (as defined above) and demonstrates a moderate or markedly improved global assessment or improved NYHA class.
3. Unchanged: The patient has not improved or worsened.

Prespecified secondary end points included the time to first HF hospitalization or death and ventricular pacing percentage.

**Statistical analysis**

CRT responses were predefined to be compared among subgroups dichotomized at the median RV-LV value. In addition, receiver operating characteristic (ROC) curves were constructed to identify the optimal cutoff to maximize the predictive value of a dichotomized RV-LV delay. The optimal cutoff equaled the maximum of Youden’s index j, calculated from the ROC data as the cutoff with the greatest sum of sensitivity and specificity (j = sensitivity + specificity − 1). The ROC curve for the primary end point of the clinical composite score was obtained from a logistic regression model. For the secondary end point of HF hospitalization or death, time-dependent ROC curves at 6 and 12 months were constructed using an inverse probability of censoring weighting approach.

Multivariate regression models were used to analyze the association between RV-LV and CRT response, adjusting for baseline covariates including age, sex, coronary artery disease, QRS morphology (left bundle branch block [LBBB] or non-LBBB), QRS duration, NYHA, LVEF, and LV lead placement. RV-LV (dichotomized at the median) was also analyzed as a predictor of response in univariate regression models separately for prespecified subgroups of patients. Heterogeneity of the effect of the RV-LV interval on CRT response by subgroup was formally tested by fitting an interaction term in logistic regression models, with RV-LV interval and the covariate of interest (QRS morphology, QRS duration, coronary artery disease, sex, age, NYHA classification, and LV lead placement) assessed as predictors of response. Logistic regression modeling was performed for the analysis of primary end point of clinical composite score, treating a worsened clinical composite score as the outcome; Cox proportional hazards modeling was performed for the secondary end point of first HF hospitalization or death. To assess for a potential nonlinear relationship between RV-LV and first HF hospitalization or death, a restricted cubic spline Cox regression analysis was used with median RV-LV interval as the reference and adjusted for age, sex, coronary artery disease, LBBB, QRS duration, NYHA, LVEF, and LV lead placement.

Continuous variables were compared using t tests. Discrete variables were compared using Fisher exact, Pearson χ², and Cochran-Armitage trend tests. A P value of <.05 was considered statistically significant. Data are presented as mean ± SD or number (%) of patients unless noted otherwise. SAS version 9.3 (SAS Institute Cary, NC) was used for statistical analysis.

**Results**

**Patient population**

A summary of the baseline clinical characteristics of the 1342 patients in this study is given in Table 1. They were typical of the general population with advanced HF receiving CRT, with primarily late middle-aged men with LBBB. A majority of patients had underlying ischemic heart disease, and the mean unpaced QRS duration was 158 ms.

**Interventricular delay**

The mean RV-LV delay was 69 ± 59 ms. The median delay was 67 ms with interquartile ranges being 40–100 ms. This is similar to the RV-LV measurements recently reported in a separate multicenter trial of subjects with NYHA class III HF using the same methodology (mean 68 ms; median 70 ms), demonstrating the reproducibility of this measure. The RV-LV duration did not differ by randomization groups in the PEGASUS (P = .95), so these subgroups were pooled as noted above. Examples of short and long RV-LV delays from 2 patients are shown in Figure 1. RV activation preceded LV activation in a vast majority of subjects (N=1236, 92%), as expected in the presence of LV dilation and predominantly LBBB.

The baseline characteristics of the patient population grouped by interventricular (RV-LV) delay are summarized in Table 1. There were some significant differences among subgroups, most notably male sex and ischemic etiology of
HF were more common in the short RV-LV delay subgroup; in addition, QRS duration was shorter and the proportion of LBBB was less common in this subgroup. To assess the clinical predictors of the interventricular delay in more detail, a multivariate analysis was performed using RV-LV duration as a continuous variable. This analysis demonstrated that female sex, LBBB, and longer QRS duration were independent predictors of RV-LV duration.

**CRT responses**

The primary end point of the PEGASUS was the clinical composite score. These results are presented in Figure 2 for the interventricular delay groups dichotomize at the median value of the population. The distribution of responses was different for the 2 groups (Cochran-Armitage trend, \( P = .014 \)), with more patients improved and fewer worsened in the long RV-LV subgroup. Specifically, 348 (56%)
patients improved in the long RV-LV group compared with 309 (51%) patients in the short group whereas 145 (23%) vs 184 (30%) worsened, respectively. Given the imbalances in several important clinical parameters between interventricular delay groups, a multivariate analysis was performed (Table 2). The odds of a worsened clinical composite score were 22% lower for the long RV-LV group, though the comparison did not achieve statistical significance (odds ratio 0.78; \( P = .083 \)).

The time to first HF hospitalization or mortality was a prespecified secondary end point. These results are shown in Figure 3. The survival curves separate early and continue to diverge over the course of follow-up (hazard ratio 0.624; \( P = .002 \)). The estimated event-free survival rate at 1 year was 88% in the long RV-LV subgroup and 81% in the short RV-LV subgroup. A multivariate analysis was performed, similar to the analysis performed for the primary end point (Table 2). The adjusted hazard ratio remained significant (hazard ratio 0.709; \( P = .038 \)), and this measure and sex were the only independent predictors of response.

### Optimal RV-LV cutoff

The median value of RV-LV delay (67 ms) was predefined to group the cohort for the primary analyses. Further analysis was performed to assess the optimal cutoff to maximize response differences between long and short subgroups. The ROC curves are shown in Figure 4. The optimal cutoff for the primary end point of clinical composite score was 63 ms. For the secondary end point of HF hospitalization or death, the optimal cutoffs at 6 and 12 months were 65 and 62 ms, respectively. The overall optimal cutoff of 63 ms was selected, equal to the optimal cutoff for the primary end point and in the optimal range of 62–65 ms for the secondary end point. The results obtained from analyses using the optimal cutoff showed only minor improvement compared with using the median value to dichotomize the population. Using the optimal cutoff, for the primary end point of CRT response, 360 (56%) patients improved in the long RV-LV group compared with 297 (N = 51%) in the short group whereas 150 (23%) vs 179 (31%) worsened, respectively (\( P = .01 \)). Freedom from HF hospitalization or death was significantly greater in the long RV-LV subgroup than in the short subgroup (hazard ratio 0.622; \( P = .002 \)). For the quality of life end point, the improvement in quality of life was greater in the long RV-LV groups (implantation to 6 weeks: 20 vs 18 point improvement, \( P = .11 \); implantation to 6 months: 23 vs 21, \( P = .14 \); implantation to 12 months: 25 vs 21, \( P = .03 \)).

To provide more granularity to the relationship between interventricular delay and CRT response, the measure was treated as a continuous variable. A spline analysis was performed as shown in Figure 5 for the end point of time to first HF hospitalization or death, which is the most common CRT end point in large multicenter trials. In this analysis, the response is normalized for the median RV-LV interval of 67 ms and corrected for differences in baseline characteristics. Interestingly, there is little change in response as interventricular conduction shortens. However, there is a

### Table 2 Multivariate models of the predictors of a worsened clinical composite score (CCS) and the composite end point of heart failure hospitalization (HFH) or death

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary end point (worsened CCS)</th>
<th>Secondary end point (death/HFH)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>RV-LV interval ≥67 ms vs &lt;67 ms</td>
<td>0.78 (0.59–1.03)</td>
<td>0.71 (0.51–0.98)</td>
</tr>
<tr>
<td>Age (per 5 y)</td>
<td>1.03 (0.97–1.09)</td>
<td>1.05 (0.98–1.12)</td>
</tr>
<tr>
<td>CAD vs no CAD</td>
<td>1.08 (0.82–1.44)</td>
<td>1.22 (0.88–1.70)</td>
</tr>
<tr>
<td>LBBB vs non-LBBB</td>
<td>0.90 (0.67–1.20)</td>
<td>1.05 (0.76–1.46)</td>
</tr>
<tr>
<td>LVEF (per 1%)</td>
<td>1.00 (0.98–1.02)</td>
<td>1.00 (0.98–1.02)</td>
</tr>
<tr>
<td>Male vs female</td>
<td>1.28 (0.96–1.72)</td>
<td>1.43 (1.00–2.04)</td>
</tr>
<tr>
<td>NYHA class IV vs class III/II</td>
<td>1.19 (0.70–2.05)</td>
<td>1.52 (0.89–2.59)</td>
</tr>
<tr>
<td>Posterior/lateral vs anterior/septal LV lead position</td>
<td>0.99 (0.62–1.61)</td>
<td>0.69 (0.43–1.10)</td>
</tr>
<tr>
<td>QRS duration (per 10 ms)</td>
<td>0.98 (0.93–1.03)</td>
<td>0.95 (0.90–1.00)</td>
</tr>
</tbody>
</table>

\( CAD = \) coronary artery disease; \( LBBB = \) left bundle branch block; \( LV = \) left ventricular; \( LVEF = \) left ventricular ejection fraction; \( NYHA = \) New York Heart Association.
monotonic improvement in response as RV-LV interval increased above 67 ms.

Subgroup analysis
Certain subgroups have been shown to respond better to CRT in previous clinical trials. Most commonly, QRS duration and morphology, sex, age, and etiology of HF are significant predictors of response. To better understand the effect of interventricular electrical delay in these subgroups, logistic regression analysis was performed. The Forest plots of the results of these analyses are shown in Figure 6. For both the proportion of subjects who worsened by clinical composite score (Figure 6A) and the odds ratio of death or HF hospitalization (Figure 6B), all subgroups showed a greater response to CRT with longer RV-LV delay. For both measures the only significant interaction was for sex, with a greater effect of interventricular delay on response rates in women.

Discussion
CRT has been shown to promote reverse remodeling, improve clinical outcomes, and reduce mortality among patients with HF with a reduced ejection fraction and QRS prolongation. Despite the proven benefit of this therapy, the nonresponder rate has remained problematic, despite newer atrioventricular delay optimization algorithms and anatomically guided lead placement.23 This has led to updated guidelines focusing more on patient selection guided by QRS duration and morphology rather than intraoperative parameters.24,25 However, recent studies of LV lead placement in areas of late electrical or mechanical delay have shown the importance of lead position on outcomes.13–19,26,27 Previous studies in diverse populations using the QLV interval as a measure of LV electrical delay demonstrated the predictive value of this measure for a variety of end points including hemodynamic response, reverse remodeling, and clinical outcome with CRT.13–16 We now show that RV-LV duration is also a strong independent predictor of clinical outcomes. To our knowledge this is the first study to demonstrate the association of any measure of LV lead electrical delay to predict clinical response in a multicenter clinical trial. Moreover, it is by far the largest study to date evaluating electrical delay (ie, QLV or RV-LV duration).
The association of RV-LV duration with CRT clinical response was robust and present for quality of life, clinical composite score, and the composite of HF hospitalization and mortality. The magnitude of response appears small at first inspection. However, this likely reflects, in part, the short duration of the trial. For instance, the 7% absolute reduction in time to first hospitalization or death at 1 year compares favorably with the reductions noted with CRT vs no CRT in many major pivotal trials.\(^2\)–\(^5\),\(^28\) Unfortunately, longer-term follow-up was not performed in this cohort, as the PEGASUS was initially designed to assess the effects of atrial programming strategies.

The association of interventricular delay was observed in all major subgroups, indicating that even parameters associated with traditionally lower CRT response rates, such as non-LBBB or QRS duration <150 ms, a longer interventricular delay was associated with a better response. QRS morphology and duration were predictive of RV-LV duration as noted above, so it is intriguing to speculate that the higher nonresponder rates observed in the presence of non-LBBB and QRS duration <150 ms are due to a decreased probability of sufficiently long electrical delay at anatomically guided lead positions. In support of this hypothesis, the proportion of subjects with RV-LV duration below the median value was higher in the non-LBBB cohort than in subjects with LBBB (74% [N=320] vs. 39% [N=351]), respectively; \(P < .001\). Whether the proportion of patients with non-LBBB electrocardiographic morphology with a long RV-LV time can be increased with less traditional LV lead locations will require further study.

Patients with HF and with QRS prolongation often have LV conduction delay, most commonly LBBB. One mechanism for the benefit of CRT is to restore electrical synchrony by preexciting the delayed LV area to achieve more synchronous interventricular electrical activation. Whereas patients with longer QRS duration and LBBB tend to have longer mean interventricular delay, RV-LV duration remains an independent predictor of response after adjusting for QRS duration and conduction disorder type. This observation again highlights that the potential importance of direct measurements of the timing of LV activation may be superior to simply using anatomic positions to guide LV lead placement.

The finding of longer interventricular delay among patients with LBBB or increased QRS duration is not surprising. However, the observations that RV-LV duration was greater in women and that there were significant interactions of sex and RV-LV duration for both clinical end points were unexpected. Women have been shown to respond better to CRT in many studies\(^29\), including the present analysis. The improved CRT response in women is not simply due to a higher prevalence of LBBB and nonischemic etiology, as sex remains an independent predictor of response in large studies.\(^29\),\(^30\) Our results suggest that a possible mechanism is that interventricular duration is more important in women than in men. The underlying cause of this observation is not clear, but several possible explanations are that women intrinsically have longer RV-LV times or that coronary sinus venous anatomy in women facilitates lead placement with longer interventricular delay.

**Clinical implications**

Reducing the nonresponder rate continues to be an important goal of CRT. Previous studies have demonstrated that interventricular duration, as measured by the RV-LV time predicts the magnitude of LV reverse remodeling.\(^17\),\(^19\) We now show that the RV-LV interval is strongly associated with clinical outcomes including the composite end point of HF hospitalization or death. These results support a strategy of evaluating interventricular electrical delay at the time of LV lead implantation and consider repositioning or, in the case of a quadripolar lead, using a different site/electrode position.
with longer electrical delay for pacing when short intervals are observed with the goal of achieving the longest possible RV-LV interval. The spline analysis suggests that the magnitude of response continues to increase at even longer interventricular delays, so maximizing RV-LV duration should improve outcomes. Validation of these findings with a randomized trial of LV lead placement guided by LV delay is warranted as the present results were observational. Although the emphasis on CRT lead placement has been focused on the LV lead, RV-LV time can also be altered by repositioning the RV lead. The importance of anatomic RV lead position could not be assessed in this study because a vast majority of such leads were placed in the apex. Consequently, further study is warranted to assess whether a strategy of placing RV leads to maximize interventricular delay would improve outcomes. This may be particularly important for patients with non-LBBB electrocardiographic morphology or with limited coronary sinus targets where repositioning of the LV lead may not be feasible.

Study limitations
This study should be interpreted in light of several methodological limitations. The cohort studied had advanced HF, so it is unknown whether these observations apply to milder HF. Follow-up in the PEGASUS was only 1 year, so the effect of interventricular delay with long-term CRT is unknown. It is noteworthy that the pivotal long-term studies of CRT showed significant improvements in outcomes in the first year of therapy with subsequent continued improvement over time. Intrinsic RV-LV duration measurements can only be performed in patients with intact atroventricular conduction, so this approach is not relevant to guide lead position in patients with heart block or with chronic RV pacing. Finally, maximizing interventricular delay was not prespecified for lead placement in the PEGASUS.

Conclusion
The PEGASUS was a large multicenter randomized trial of patients undergoing CRT-defibrillator implantation with blinded assessment of end points. We show that the RV-LV interval is a strong and independent predictor of clinical response with CRT. Based on these results, measuring RV-LV time at implantation may help to identify optimal pacing sites.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2017.10.016.

References
References