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 ($<$67 ms) and long ($\geq$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

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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,[1,6–8] 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

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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,[20,21] 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.[20–22] 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 χ^2, 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),[19] 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