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Association between QRS duration and outcome with cardiac resynchronization therapy: A systematic review and meta-analysis

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Abstract

Purpose: We conducted a systematic review and meta-analysis of randomized and observational studies to evaluate the associations between QRS duration (QRSd) at baseline or in follow-up and outcomes with cardiac resynchronization therapy (CRT).

Methods: We searched online databases to December 2010 and included 6 randomized controlled trials (RCTs) and 38 observational studies. Outcomes included clinical/functional response, left ventricular (LV) remodeling, hospitalizations and mortality.

Results: In RCTs, a benefit of CRT was evident only in patients with QRSd >150 ms. In observational studies, those meeting either clinical or remodeling CRT response definitions had both wider pooled baseline QRSd and significantly more QRS narrowing with CRT than non-responders.

Conclusions: RCTs demonstrate that benefit with CRT appears restricted to those with baseline QRSd wider than 150 ms. Both wider baseline QRS and more QRS narrowing are associated with CRT response in observational studies. Electrocardiographic QRSd plays an important role in CRT patient selection and follow-up.

Keywords: Cardiac resynchronization therapy; Heart failure; Electrocardiogram; QRS duration; Meta-analysis

Introduction

Cardiac resynchronization therapy (CRT) is an important treatment for selected patients with heart failure due to left ventricular (LV) systolic dysfunction.[1] Based on data from landmark randomized trials demonstrating improvements in symptoms, cardiac remodeling and survival, CRT is considered as standard therapy for patients with symptomatic heart failure (New York Heart Association (NYHA) class II to IV limitation, LV ejection fraction (LVEF) values ≤0.35, sinus rhythm and a widened QRS duration (QRSd).[2–4] While previous guidelines recommended a minimum QRSd of 120 ms in all patients, recent European and American guidelines reserve the strongest level of recommendations for patients with a QRSd ≥ 150 ms.[3,4] Even in contemporary series, at least one-third of patients meeting the selection criteria do not clearly benefit from CRT, and are termed non-responders.[5,6] Efforts to reduce non-response to CRT are vital given its cost and complexity. Among the potential predictors of response, much work has focused on the use of imaging to identify LV dyssynchrony with greater precision than that afforded by the surface ECG. Unfortunately, promising initial results with echocardiographic measures of mechanical dyssynchrony were not replicated in a prospective multi-center study.[7] In contrast, while surface ECG features such as QRS duration (QRSd) and QRS morphology for prediction of response are known to have limitations,[6,8–11] they are inexpensive, are widely available

Abbreviations: 6MWD, 6-min walk distance; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; QRSd, QRS duration; RCT, randomized controlled trials.

Trial Acronyms: CARE-HF, Cardiac Resynchronization in Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; PATH-CHF II, Pacing Therapies in Congestive Failure II; RAFT, Resynchronization/Defibrillation in Ambulatory Heart Failure Trial; REVERSE, REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction.

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and may provide an adequate estimate of dyssynchrony in many patients. To address this uncertainty we performed a systematic review and meta-analysis of published clinical reports evaluating the association between ECG QRSd and measures of response in patients implanted with CRT.

Methods

Search strategy

We developed search strategies for Ovid MEDLINE and EMBASE databases in consultation with a research librarian. These searches combined the clinical themes of electrocardiography/QRS and CRT, with terms used to identify human clinical studies (see the Data Supplement for the full MEDLINE search strategy). We included articles published in any language from 1984 to December 2010. To improve sensitivity we hand-searched bibliographies of relevant review articles.

Review details

Three reviewers (A.R.B., S.B.W., D.V.E.) independently screened titles and abstracts of all records. Articles were selected for full-text review if any of us believed that the study addressed an association between clinical CRT outcomes and QRSd.

On full-text review we included articles that (1) were original clinical reports studying patients with systolic heart failure undergoing CRT; (2) included baseline (prior to CRT) ECG data; (3) had a sample size ≥ 25 and follow-up ≥ 3 months; and (4) reported on at least one relevant endpoint. These endpoints included death, heart transplant, heart failure hospitalization, or CRT response defined using changes in any of the following: NYHA class, 6-min walk distance, quality of life measures, exercise tolerance, or echocardiographic measures (LVEF or LV end-systolic volume [ESV]).Duplicative reports were excluded. Reports meeting all criteria were further categorized as follows: (1) parallel-arm randomized clinical trials of CRT versus active control (medical therapy with or without an implantable defibrillator) presenting outcomes stratified by baseline QRS duration; (2) observational studies presenting CRT outcomes stratified by baseline QRS duration; and (3) observational studies comparing baseline and follow-up QRSd in patients with and without a given CRT outcome. Data from these complementary study types were analyzed separately.

For each included article, we extracted study-specific eligibility criteria, patient demographics, definition(s) of CRT outcomes, and patient groupings. Where effect estimates and associated confidence limits for QRSd subgroups were not stated, we estimated them from published forest plots using digital calipers. We also extracted key indicators of study internal validity using a published framework.[12]

Statistical analysis

Continuous data were recorded as mean ± standard deviation (SD). We calculated the weighted mean difference (WMD) in baseline QRSd and in the change in QRSd with CRT in responders versus non-responders for each included study. We used Cochran's Q statistic to assess between-study heterogeneity. When pooling of study results was deemed to be appropriate, we used Der Simonian and Laird random-effects models to calculate the pooled effects when a significant heterogeneity was identified, otherwise, Mantel–Haenszel fixed-effects models were used. We also performed stratified analyses for this outcome based on the definition of CRT response used in the component studies (clinical response, LV remodeling, or their combination). p-Values <0.05 were considered statistically significant. Analyses were performed using Stata version 11.1 (Stata Corp., College Station, TX, USA).

Results

Literature search

The results of our literature search and study selection are illustrated in e-Figure 1 (Data Supplement).The database search and bibliography screen yielded 6487 citations, of which 6212 were excluded in the first screen. Of 275 reports undergoing full-text review, 44 were included. Reasons for exclusion of the others are summarized in e-Figure 1. Of included studies, 6 were RCTs that stratified patient outcomes by QRSd.[13–18] The remaining 38 studies were observational: 34 compared ECG characteristics in CRT responders and non-responders (response grouping),[9,10,19–50] while 4 compared CRT outcomes grouped patients according to strata of QRSd (QRS grouping).[51–54]

Study characteristics

Study and patient characteristics are outlined in Table 1. The six RCTs, five with a parallel-arm design, and one short-term crossover trial, included a total of 6647 patients with a mean age of 66 years, 24% females, and all with baseline QRSd ≥ 120 ms. Patients had a mean baseline left ventricular ejection fraction (LVEF) of 0.23 and all optimal use of HF medications was required in all studies. The mean baseline QRS duration was 158 ms.

The 38 observational studies included a total of 4715 patients. Overall, the mean age was 66 years, 25% were female and 52% had ischemic cardiomyopathy. The mean baseline LVEF was 0.24 and the mean 6MWD was 283 m. The QRSd inclusion criteria varied between <120 ms and ≥ 150 ms. In the four QRS-grouped studies, the threshold used to define wide QRS was ≥ 120 ms in three,[51–53] and ≥ 130 ms in one.[54] The nine studies that did not report QRSd inclusion criteria had a similar weighted mean QRSd (159 ms) to other studies.

Study quality

Key factors influencing study quality are summarized in E-Table 1 (Data Supplement). Loss to follow-up was appropriately quantified in most studies. Blinding of outcome assessors was less frequent in the response-grouped studies than in other study designs. As expected, baseline differences in prognostically important variables were frequent in the observational studies.