Review

Should women have different ECG criteria for CRT than men?

Noel S. Lee (MD), Felice Lin (MD), Ulrika Birgersdotter-Green (MD)*

Division of Cardiovascular Medicine, University of California, San Diego, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 10 December 2016
Accepted 12 December 2016
Available online 31 January 2017

Keywords:
Cardiac resynchronization therapy
Heart failure
Left bundle-branch block
Gender differences
QRS duration

ABSTRACT

One of the key aspects of heart failure management is whether patients should be considered for device therapy. Clinical trials, which have employed QRS duration and morphology as measures of left ventricular dyssynchrony, have demonstrated the morbidity and mortality benefit of cardiac resynchronization therapy. Women, however, are underrepresented in these trials, the basis of which current guidelines and standards of care are derived. Despite low enrollment of women, several studies highlight the statistically significant improvement in risk reduction that women gain from cardiac resynchronization therapy compared to men. This review discusses the foundation for current guidelines and the building evidence that women may reap more benefit from cardiac resynchronization therapy than men. Given these data, a more individualized approach should be considered in prescribing this device therapy in the future, particularly in women.

© 2017 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Contents

Introduction .......................................................................................................................... 1
Background ......................................................................................................................... 1
  Patient selection: QRS duration ...................................................................................... 2
  Patient selection: QRS morphology ............................................................................... 2
Gender differences ............................................................................................................. 3
Discussion .......................................................................................................................... 4
Conclusion .......................................................................................................................... 5
Funding ............................................................................................................................... 5
References ......................................................................................................................... 5

Introduction

Cardiac resynchronization therapy (CRT) has proven efficacious in clinical trials in improving quality of life and reducing mortality and hospitalizations for patients with advanced heart failure. Women, despite composing a large percentage of the heart failure population, are underrepresented in these trials, the basis of which current guidelines and standards of care are derived. Recent studies examining the differences in gender outcomes from CRT suggest that women gain greater benefit from these devices than men. This article carefully reviews pivotal evidence in CRT that ultimately advocates for a more individualized approach in prescribing this therapy, particularly in women.

Background

QRS prolongation >120 ms, usually due to left bundle-branch block (LBBB), is found in about one-third of patients with systolic heart failure [1]. This conduction delay causes abnormal septal motion leading to a pressure gradient between the ventricles and therefore ventricular dyssynchrony [2]. Hemodynamic consequences include decreased left ventricular filling time, diminished stroke volume, and mitral regurgitation. Thus, ventricular dyssynchrony adds insult to injury in an already failing left ventricle (LV). Indeed, a wide QRS complex has been associated with increased mortality [3].

* Corresponding author at: 9300 Campus Point Drive, Mail Code 7411, La Jolla, CA 92037-7411, USA. Fax: +1 858 657 5314.
E-mail address: ubgreen@ucsd.edu (U. Birgersdotter-Green).

http://dx.doi.org/10.1016/j.jcc.2016.12.008
0914-5087/© 2017 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
The primary goal of CRT is to restore synchrony and help optimize mechanical functioning of the LV in patients with congestive heart failure. Randomized clinical trials have demonstrated the effectiveness of CRT in improving quality of life, functional status, and exercise capacity [4]; enhancing reverse remodeling [5]; and reducing mortality and hospitalization [6,7]. Compared to optimal pharmacologic therapy alone, CRT not only benefits patients with advanced New York Heart Association (NYHA) class III or IV heart failure [6], but also patients with mild-to-moderate heart failure (NYHA class II or III) and severe LV dysfunction [7].

**Patient selection: QRS duration**

Early clinical trials in CRT laid the foundation for CRT implantation guidelines by using QRS duration as a gauge of ventricular dyssynchrony (Fig. 1). Only 15 years have passed since the presentation of the first large, prospective, randomized double-blind trial of CRT and subsequent US Food and Drug Administration approval of CRT devices in 2001. The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study examined 453 patients with moderate or severe (NYHA class III or IV) heart failure symptoms with an ejection fraction (EF) of ≤35% and a QRS ≥130 ms [8]. Patients were randomly assigned to a CRT or control group and followed for 6 months while standard pharmacologic therapy was continued. Patients randomized to CRT showed statistically significant improvements in the 6-min walking test ($p = 0.005$), functional class ($p < 0.001$), quality of life ($p = 0.001$), and EF (+4.6% vs. –0.2%, $p < 0.001$), as well as a relative decrease in hospitalization [8].

Like MIRACLE, other early trials also used QRS duration inclusion criteria to study CRT benefits, with patient QRS duration ranging from 120 to 150 ms [6,9–15]. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2008 guidelines for device-based therapy reflected these studies, specifying a QRS duration of 120 ms as part of a Class I indication for CRT for patients with severe systolic heart failure [16]. International groups took a similar approach [17,18].

**Patient selection: QRS morphology**

Later clinical trials including MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) [19], REVERSE (RESynchronization reVeVerses Remodeling in Systolic left VEntricular dysfunction) [20], and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) [7], which were designed to assess CRT outcomes in NYHA Class II patients, confirmed that patients with a low EF and wide QRS complex but more moderate symptoms than previously studied would also benefit from CRT. Subgroup analyses from these studies further revealed that 1) the longer the QRS duration, the more beneficial CRT is likely to be [7,19]; and 2) patients with LBBB had greater benefit than those with other non-LBBB intraventricular conduction delays [7,21].

MADIT-CRT was a multicenter trial of 1820 patients with EF ≤30%, QRS > 130 ms, and NYHA Class I or II symptoms [19]. The trial concluded that CRT with defibrillator (CRT-D) reduced the rate of mortality or heart failure events compared to ICD alone [hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.52–0.84; $p = 0.001$] during a mean follow-up of 2.4 years [19]. The prespecified subgroup analysis focusing on QRS duration revealed that patients with a QRS > 150 ms had a significant benefit with CRT (HR 0.48; 95% CI 0.37–0.64) not found in those with a QRS < 150 ms (HR 1.06; 95% CI 0.74–1.52) ($p = 0.001$) [19]. A later analysis of the MADIT-CRT patients divided by QRS morphology suggested that the benefit of CRT-D was limited to patients with LBBB: the LBBB patients treated with CRT-D experienced a 53% reduction in the risk of mortality or heart failure events compared to the LBBB patients treated with ICD only (HR 0.47, $p < 0.001$) [21]. The non-LBBB patients did not derive clinical benefit from CRT-D [21].

Similar in study size and patient characteristics, RAFT also found that the combination of CRT with ICD decreased death and heart failure hospitalization rates over a mean follow-up of 40 months [7]. Again, patients with QRS > 150 ms showed a more marked benefit compared to those with QRS < 150 ms (HR 0.59; 95% CI 0.48–0.73; $p = 0.002$). Subgroup analysis also revealed a greater benefit in patients with LBBB compared to other conduction delays ($p = 0.046$) [7].

Later, a meta-analysis of four randomized controlled trials examined the effect of CRT on composite clinical events in patients with LBBB and non-LBBB, substantiating the finding that patients with LBBB have better outcomes from CRT [22]. A total of 5356 patients (3009 CRT vs. 2347 controls) from COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), CARE-HF (Cardiac Resynchronization in Heart Failure), RAFT, and MADIT-CRT were included. Patients with LBBB randomized to CRT had a significant risk reduction in heart failure.

Fig. 1. Timeline of clinical trials in device therapy.
CR, cardiac resynchronization; Epi, epicardial; LV, left ventricular; X-over, crossover.
hospitalizations and death with a risk ratio of 0.64 (95% CI 0.52–0.77; p < 0.001) [22]. In contrast, no benefit was obtained with CRT regardless of NYHA functional class in patients with non-LBBB morphology [22].

Considering these studies and other accumulating evidence, the ACC, AHA, and HRS modified the Class I indication for CRT in 2012 to incorporate both QRS duration and QRS morphology to guide which patients should have CRT devices placed. The updated guidelines also expanded patient subsets to include not only patients with NYHA class III and IV symptoms, but also those with NYHA class II symptoms [23].

Gender differences

Interestingly, in examining these trials more closely, one may ask: who benefits the most? The answer could be women. MADIT-CRT and RAFT both demonstrated benefit of cardiac resynchronization in wide QRS complexes with a LBBB morphology. Both studies also convincingly argue that these clinical outcomes are associated with gender differences.

For example, prespecified subgroup analysis in the primary publication of MADIT-CRT noted that CRT-D therapy vs. ICD alone was associated with increased benefit in reducing risk of death or nonsustained ventricular tachycardia in women (HR 0.37; 95% CI 0.22–0.61) compared to men (HR 0.76; 95% CI 0.59–0.97; p = 0.01) [19].

A further study was done to examine the factors related to sex-specific outcomes [24]. Overall, women had better results from CRT-D vs. ICD alone than men, with a significant 69% reduction in death or heart failure (HR 0.31, p < 0.001 vs. HR 0.72, p < 0.01; interaction p < 0.01). Whereas women had a significant reduction in all-cause mortality (HR 0.28, p = 0.02), men did not (HR 1.05, p = 0.83). QRS > 150 ms and LBBB were identified as factors related to sex-specific outcomes: both women with QRS > 150 ms and women with LBBB had significant reductions in mortality (HR 0.18, p < 0.05 and HR 0.22, p = 0.01, respectively), neither of which was evident in men. Not only did women receiving CRT-D therapy have significantly better outcomes than women receiving ICD therapy, but also than men receiving ICD therapy and men receiving CRT-D therapy during an average 2.4-year follow-up [24].

These results, combined with the data supporting lack of any CRT-D benefit in patients without LBBB, spurred another substudy of MADIT-CRT that assessed 1) the long-term clinical outcomes of CRT-D vs. ICD alone, and 2) the sex-specific benefit of CRT-D [25]. The study included the 1281 patients from MADIT-CRT who had LBBB morphology, of which 394 (31%) were women. Over the mean 5.6-year follow-up, results again indicated mortality benefit in these patients with CRT-D vs. ICD alone (HR 0.49, p = 0.038 in women; HR 0.7, p = 0.032 in men). Women had a more pronounced benefit, with a significant 71% decrease in the composite endpoint of heart failure hospitalizations and death (HR 0.29, p < 0.001) compared with a 41% reduction in men (HR 0.59, p < 0.001).

This study of LBBB patients also found QRS duration to be a factor in sex-specific outcomes. Interestingly, when the effect of QRS duration was considered by sex, women with CRT-D had a significant decrease in risk of heart failure or death with QRS < 150 ms (HR 0.32; 95% CI 0.14–0.76, p < 0.01) and ≥150 ms (HR 0.27; 95% CI 0.17–0.45, p < 0.001) compared with ICD only. Men, on the other hand, only showed a significant reduction in heart failure or death with QRS ≥ 150 ms (HR 0.55, 95% CI 0.41–0.73; p < 0.001) [25]. Additionally, within the QRS ≥150 ms and <150 ms subgroups, women had a greater magnitude of risk reduction than men, with significant sex-by-treatment interaction (p < 0.05 for both) [25].

Data from another study support the notion that women respond equally well regardless of whether QRS is ≥ or <150 ms, whereas men primarily respond with QRS duration ≥150 ms. Varma et al. evaluated QRS duration and gender on CRT effect in patients with dilated non-ischemic cardiomyopathy [26]. A significantly higher response rate was seen in the population with QRS ≥150 ms compared to <150 ms (76% vs. 58%, respectively, p = 0.009) (A). When individuals within the QRS groups were further stratified by gender, women demonstrated a high response rate regardless of having QRS <150 ms or ≥150 ms, whereas men showed most response with QRS ≥150 ms (B).

CRT, cardiac resynchronization therapy. Reprinted with permission from Varma et al. [26].

The prespecified subgroup analysis for sex in RAFT also found a trend toward benefit with CRT in women compared to men (p = 0.09) [7]. Despite this evidence, the ability of these trials to definitively reflect real-world differences in CRT-D outcomes in men and women was limited. Device implantation trials, as well as cardiovascular trials in general, have had a very low inclusion rate of women. The study populations of MADIT II, SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), COMPANION, and CARE-HF, for example, were about 85%, 77%, >65%, and >70% men, respectively (Fig. 3) [6,27–29]. Approximately 80% of the population in RAFT were males [7].

Thus, Zusterzeel et al. took a large real-world population of >75,000 patients (68% men) from the National Cardiovascular Data Registry Implantable Cardioverter Defibrillator Registry (NCDR)
registry with NYHA class III or IV heart failure, reduced left ventricular EF, and QRS ≥ 120 ms to examine sex-specific death risk with CRT-D vs. ICD [30]. Using propensity score analysis, the overall mortality rate in the total weighted cohort of CRT-D and ICD patients was lower in women than in men. In the sex categories, after a mean follow-up of 2.5 years, women with CRT-D had a lower mortality risk than women with ICD (absolute difference 11%; HR 0.77; 95% CI 0.72–0.82; \( p < 0.001 \)). Men with CRT-D also had a lower mortality rate (albeit much less evident) than those with ICD (absolute difference 7%; HR 0.88; 95% CI 0.85–0.92; \( p < 0.001 \)). This mortality difference between sexes was significant (\( p < 0.001 \)) [30].

The real-world NCDR registry study also highlighted the lower mortality risk with CRT-D than with ICD in both men and women with LBBB. Women had a more pronounced reduction in death risk, though (absolute difference 11%, HR 0.74, 95% CI 0.68–0.81), compared to men (absolute difference 9%, HR 0.84, 95% CI 0.79–0.89) (interaction \( p = 0.025 \)) [30].

**Discussion**

The pressing question is: why do such gender differences exist in CRT outcomes? Some theories abound including whether the higher proportion of nonischemic cardiomyopathy and smaller left ventricular diameter in women – both are which are predictors of CRT response – may contribute [31]. Perhaps men, who have larger diameters, may simply be demonstrating the natural progression of heart failure in which after a certain point, reverse remodeling and response to CRT diminishes or ultimately becomes unlikely [32].

Another possible explanation for the observed gender differences in CRT response is the intrinsic difference in baseline QRS duration between men and women (Fig. 4) [33]. QRS widening ≥ 120 ms occurs in 14–47% of heart failure patients [1]. In MADIT-CRT, the inclusion criteria of QRS ≥ 130 ms was used for both women and men [19]. Normally, women have QRS complexes that are about 10 ms shorter than in men [34]. Thus, for any given QRS ≥ 130 ms, women might demonstrate relatively more conduction disturbance and electrical dyssynchrony than men, possibly explaining why CRT is more beneficial in women.

Furthermore, LBBB has been associated with better CRT response [21,22]. Men may have an increased prevalence of false positive LBBB, as studies have shown that roughly one-third of patients with the conventional LBBB morphology actually have normal transeptal activation that does not in fact support a true LBBB [35]. LBBB in men is also frequently associated with pathologies such as left ventricular hypertrophy that widen QRS but do not cause electrical dyssynchrony [36]. Since women have smaller ventricles and a shorter baseline QRS [37], they may also have a true LBBB at a shorter QRS duration than men.

One may then ask about the benefit of CRT in shorter QRS durations. Most patients with heart failure have narrow QRS complexes and do not fall into the MADIT-CRT inclusion criteria. Do heart failure patients with echocardiographic evidence of left ventricular dyssynchrony yet no electrocardiographic evidence of electrical conduction delay benefit from CRT? Echo-CRT (echocardiography guided cardiac resynchronization therapy), a randomized controlled trial, sought to answer this question. The study enrolled NYHA class III and IV patients with QRS < 130 ms and echocardiographic evidence of mechanical dyssynchrony. It was ultimately stopped for futility [38].

**Fig. 3.** Proportion of women compared to men in clinical trials in device therapy. Device implantation trials, as well as cardiovascular trials in general, have had a low inclusion rate of women.

**Fig. 4.** Distribution of baseline QRS duration and proportions of LBBB among women and men in a study by Linde et al. The percentage of women and men with QRS durations in 10 ms intervals is illustrated, as well as the proportion reported to have LBBB (hashed bars). Women had narrower QRS complexes. As QRS widened, the proportion of patients with LBBB increased in both genders, but overall, once QRS reached ≥ 120 ms, LBBB was more common in women compared with men. LBBB, left bundle branch block. Reprinted with permission from Linde et al. [33].

**Fig. 5.** Relationship of QRS duration and CRT response in REVERSE [40]. The association between clinical composite score and QRS duration was highly significant (odds ratio, 0.831 for each 10 ms increase in QRS duration; \( p = 0.0001 \)), with improved response at longer QRS durations. CRT, cardiac resynchronization therapy. Reprinted with permission from Poole et al. [41].
A prespecified subgroup analysis of the effects of sex on clinical outcomes in Echo-CRT showed no difference in overall outcomes and after multivariable adjustments [39]. However, interestingly, cardiovascular mortality increased 2.4-fold in men (HR 2.43, 95% CI 1.27–4.63, p = 0.007) compared to women (HR 0.97, 95% CI 0.24–3.93, p = 0.97). This finding was not statistically significant (p = 0.37), but overall, Echo-CRT showed a trend toward harm in men in all outcomes including heart failure hospitalizations and events, all-cause mortality, and cardiovascular hospitalizations [39].

Echo-CRT irrefutably concluded that CRT-D does not improve outcomes in men or women with narrow QRS and should not be employed in that population. Still, sorting patients into two groups by QRS duration may not be an optimal strategy in defining response to CRT given that QRS duration is a continuous scale. Data from the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial argue for this point. REVERSE was a multicenter randomized trial of 610 patients with mild heart failure who underwent CRT device implantation followed by randomization to either active CRT or to the control group [40]. The study found that baseline QRS duration was a strong predictor of reduction in left ventricular end-systolic volume index with CRT (p < 0.0001). The association between clinical composite score and QRS duration was also highly significant (odds ratio, 0.831 for each 10 ms increase in QRS duration; p < 0.0001), with improved response at longer QRS durations (Fig. 5) [40,41]. The data illustrated a progressive incremental response to CRT by increasing QRS duration without a definitive cut-off value for reverse remodeling or clinical benefit of CRT other than the usual lower limit of 120 ms.

Thus, for men, and particularly for women, CRT should not be denied solely based on a QRS of <150 ms. To account for these differences between women and men, stricter LBBB criteria have been proposed by some groups. One, for example, suggests a definition including a QRS >130 ms in women and >140 ms in men, along with mid QRS notch or slurring [36]. Others have noted that baseline QRS durations differ not only between women and men but also between races (Fig. 6) [42]. Varying benefit in CRT outcomes may then be anticipated between men and women of African and Caucasian origin when studied by QRS duration. Ultimately, although the QRS provides clinicians with an immediate practical tool, it lacks the finesse to uniformly predict response and enable individualization of the delivery of CRT. This deficiency is true for both men and women.

Conclusion

Clearly CRT benefits heart failure patients with a widened QRS and LBBB morphology. Overall more data are available on QRS duration, as this measure was used in the initial CRT clinical trials. Response to CRT appears to increase as the QRS prolongs with greatest benefit in QRS ≥150 ms. Nevertheless, clinical experience suggests that some patients with QRS <150 ms may also respond. Similarly, not all patients with QRS ≥150 ms benefit either. Recent studies have placed more emphasis on QRS morphology. These data demonstrate variability in clinical response between patients with LBBB and non-LBBB morphology.

Interestingly, women, who compose a small proportion of clinical trial populations, not only appear to have greater benefit from cardiac resynchronization than men, but a benefit that is independent of QRS duration and extends beyond the now generally accepted cut-off of ≥150 ms: benefit is highly evident in female patients with QRS <150 ms. Additionally, in patients with LBBB who receive CRT therapy, mortality is lower in women than in men.

Current guidelines recommend that all patients with QRS duration of at least 150 ms with LBBB morphology be referred for cardiac resynchronization. Given recent studies, the guidelines for CRT may need to be amended in the future to account for gender differences in clinical outcomes.

Funding

None.

References


