Cardiac Resynchronization Therapy in Women

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KEYWORDS

• Cardiac resynchronization therapy • Left bundle branch block • Women • Heart failure

KEY POINTS

- Women are underrepresented in all cardiac resynchronization (CRT) studies, in which they are typically less than 30% of the population.
- Most of the available data show that CRT produces a greater clinical benefit in women than in men.
- In several studies, women have left bundle branch block (LBBB) more frequently than men.
- Women have true LBBB at QRS durations shorter than those of men with LBBB.
- Although plausible, it is unknown whether sex differences in cardiac remodeling influence the response to CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has been studied for 2 decades, and trials conducted over this period of time have first shown that CRT enhances functional capacity, then that this improvement is due to augmentation of left ventricular (LV) systolic function, reduction in LV volumes and mitral regurgitation, and finally that this beneficial reverse myocardial remodeling achieved with CRT is associated with improved survival and fewer events in patients with heart failure (HF) with mild to severe disease.[1–5]

Studies of CRT and clinical experience have also shown that variable percentages of patients fail to improve with CRT (nonresponders), whereas some CRT recipients experience near normalization of their LV systolic function (super-responders). This diversity of responses has driven the performance of numerous studies and analyses aimed at the identification of predictors of outcomes after CRT.[6–8]

Female sex is one of the factors that has repeatedly emerged as a predictor of CRT benefit.[9,10]

However, the interpretation of the data regarding sex-specific CRT effects is hindered by many important facts: (1) There are no prospective, randomized controlled clinical trials (RCTs) specifically comparing CRT responses in male versus female patients with HF. (2) The sources of information currently available include observational retrospective studies, databases, registries, and post hoc analyses of RCT and meta-analyses. (3) Regardless of the data source, women are underrepresented in both RTCs and observational studies in which female patients are typically only 30% or less of subjects.[11,12] There are several potential causes for the low proportion of women undergoing CRT (**Box 1**). Despite the limitations inherent to all the analyses on the effects of CRT in women, sufficient and important information can be gathered from the available literature to (1) summarize the findings up to date, (2) identify

This article originally appeared in Cardiac Electrophysiology Clinics, Volume 7, Issue 4, December 2015.
Dr M.R. Costanzo receives reimbursement for travel and consulting honoraria from St. Jude Medical. The Advocate Heart Institute receives research grants from St. Jude Medical.
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Heart Failure Clin 13 (2017) 165–178
http://dx.doi.org/10.1016/j.hfc.2016.07.013
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Box 1
Potential reasons for underrepresentation of women in CRT trials

- Women have higher rates of HFpEF, for which CRT is not indicated.
- There are fewer referrals of women for CRT implant, partially because of concern for higher procedural complications.
- There are higher refusal rates to undergo CRT implant in women than in men.

Abbreviation: HFpEF, HF with preserved ejection fraction.

the gaps in our knowledge, and (3) shed light on which studies should be performed to confirm or refute the belief that women and men have differential responses to CRT.

OBSERVATIONAL STUDIES

The key findings and limitations of observational studies evaluating gender differences in response to CRT are summarized in **Boxes 2** and **3**.

In a retrospective study of 550 patients (22% women, 69% New York Heart Association [NYHA] III, 31% NYHA IV) undergoing CRT at a single center between 2000 and 2009, female sex predicted a 48% lower mortality from cardiovascular (CV) death ($P = .0051$) and all-cause mortality ($P = .0022$), a 44% decrease in the combined end point CV death/HF hospitalizations ($P = .0036$), and a 33% reduction in death from any cause/hospitalizations for major adverse CV events ($P = .0214$).[10] Compared with men, women had a 45% lower pump failure mortality rate ($P = .0330$) but similar frequency of sudden cardiac death. A decrease in LV end diastolic volume (LVEDD) by 15% or greater occurred more often in female than male patients (62% vs 44%, respectively, $P = .0051$). The rate of response to CRT, defined as improvement by 1 or greater NYHA class, 25% or greater in 6-minute walking distance, or a composite clinical score (which included these two variables plus survival free from HF hospitalizations for $\geq$1 year after implantation) was 78% and similar for both sexes. By multivariable analysis, the association between female sex and lower morbidity and mortality was independent of age, LV ejection fraction (LVEF), atrial rhythm, HF cause, QRS duration, CRT device type, NYHA functional class, and decrease in LVEDD (adjusted hazard ratio [HR]: 0.48, $P = .0086$).[10] Although these findings suggest that the factors responsible for the better outcomes may be intrinsic to female sex, they do not uncover their precise nature. In addition, the study provides data only on QRS duration but not on its configuration, making it impossible to determine if the greater benefit of CRT in women is due to a higher frequency of true left bundle branch block (LBBB), an electrocardiographic feature that underlies true dyssynchronous conduction and, therefore, predicts greater benefit from CRT.[11–17]

Results in sharp contrast with the aforementioned study emerged from another retrospective cohort analysis of 728 consecutive patients

Box 2
Key findings of observational studies evaluating sex differences in response to CRT

- Women are generally 30% or less of the study population.
- Compared with men, women typically
  - Have higher rates of
    - Nonischemic HF cause
    - LBBB configuration
    - Procedural complications
  - Have lower rates of
    - Atrial fibrillation
    - Ischemic HF cause
  - Have smaller LV volumes
- Female sex is frequently an independent predictor of greater CRT benefit after adjustment for HF cause, QRS length and configuration, atrial arrhythmias, and LV volumes.

Abbreviation: LBBB, left bundle branch block.

Box 3
Limitations of observational studies evaluating sex differences in response to CRT

- Variability in
  - End points
  - Length of follow-up
  - Definition of response to CRT
- Failure to consistently
  - Report QRS configuration (LBBB vs other conduction abnormalities)
  - Index LV volumes to body surface area

Abbreviation: LBBB, left bundle branch block.

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