Original Article

Evaluation of Gender Differences in Response to Cardiac Resynchronization Therapy in a Single Heart Center

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has a beneficial effect on clinical symptoms, exercise capacity, and systolic left ventricular (LV) performance in patients with heart failure. The objective of the current study was to evaluate whether a gender difference exists in response to CRT according to clinical indices.

Methods: Totally, 229 consecutive patients with end-stage heart failure (LV ejection fraction ≤35%), QRS duration >120 ms, and left bundle branch block configuration underwent CRT. At baseline and 6 months post-CRT, clinical and echocardiographic parameters were evaluated and followed-up was obtained for up to 6 months. The clinical alterations after CRT implantation were compared between the men and the women.

Results: The study population consisted of 229 patients [129 (56.3%) male and 100 (43.7%) female; mean age=62.90±12.97 y, and age range=9–24]. No significant difference between the men and the women regarding age was found [men=62.13±14.26 y and women=63.89±11.12 y (*P*=0.3)]. The mean of the QRS width after CRT implantation in the men and the women was 147.50±23.09 and 145±18.45 ms, respectively, and the difference between the 2 groups was significant (*P*=0.001). There was no significant relationship between sex and hospitalization (*P*=0.09). At 6 months' follow-up, LV ejection fraction in the men and the women was 18.56±6.18 and 20.78±8.96, respectively (*P*=0.1).

Conclusions: At 6 months' follow-up, most of the patients had a normal sinus rhythm. Most of the deaths were seen in the males. The men had a slightly greater QRS width after CRT implantation in than the women. The chief reasons for hospitalization and mortality were shock and heart failure decompensation. LV ejection fraction before and after CRT was significantly greater in the female patients than in their male counterparts; however, the difference was significant before the implantation. ***(Iranian Heart Journal 2019; 20(2): 13-20)***

KEYWORDS: Cardiac resynchronization therapy; CRT, QRS duration, Gender, Heart failure, Ejection fraction, Left ventricle, Cardiomyopathy

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Cardiac resynchronization therapy (CRT) is currently considered a major advance in the treatment of patients with drug-refractory heart failure (HF). Recently, several major randomized trials have shown the beneficial effects of CRT on clinical symptoms, exercise capacity, and left ventricular (LV) systolic function.[1–4] It was demonstrated in the CARE-HF trial that CRT also increased survival as compared to optimized medical therapy, and this was accompanied by a significant reduction in the number of rehospitalizations for heart failure.[4]

Further, cardiac resynchronization therapy with defibrillator (CRT-D) is also an approved treatment for patients with advanced stages of HF in the setting of a widened QRS, and this therapy leads to a reduction in symptoms, an improvement in functional capacity, and a decrease in hospitalization and mortality.[5]

It is unknown whether a gender-related difference in response to CRT exists. This is an essential issue inasmuch as numerous studies have pointed out gender differences in the presentation of coronary artery disease (CAD) and differences in response to therapy.[6-8] Accordingly, the objective of the present study was to determine whether a gender difference exists in response to CRT.

According to some studies, CRT in patients with HF and with a prolonged QRS duration imparts survival benefits.[9] Nevertheless, a significant absence of response (30%–40%) among treated patients indicates that the selection criteria require refinement.[10] Clinical experience recommends that some patients with a QRS duration of 150 ms may respond and not all patients with a QRS duration of 150ms benefit, indicating that CRT prescription according to the QRS duration dichotomization may be a blunt selection tool. Supplementary influences on the effects of CRT include ischemic disease, and, controversially, gender.[11-13]

CRT trials have assessed differing proportions of patients with these comorbidities, always with women as a minority. Later, several questions persist.[14] The recently reported randomized MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial demonstrated that patients treated with CRT-D with New York Heart Association (NYHA) functional class I and II, HF symptoms, a left ventricular ejection fraction (LVEF) of 0.30, and a QRS of 130 ms had a 34% reduction in the risk of HF or death, whichever came first, when compared with patients treated with an implantable cardioverter-defibrillator (ICD).

METHODS

Totally 229 cases with CRT implantation (NYHA III-IV), QRS>120 ms, and resistance to drug treatment during the preceding 3 years underwent CRT implantation in our tertiary care center. The patients' data were extracted from documents, and the patients were followed up through telephone contacts and a comprehensive questionnaire. Variables and clinical characteristic were included in the questionnaire—including the underlying heart disease (ischemic cardiomyopathy [ICMP] and non-ischemic cardiomyopathy [NICMP]), the NYHA class before and after CRT implantation, echocardiographic data before implantation and 6 months thereafter (defined as LVEF, left ventricular end-diastolic volume [LVEDV], and left ventricular end-systolic volume [LVESV]), and finally the data of CRT implantation and the duration of having it. The patients' status (death or alive), the cause of death (heart failure, arrhythmias, and others), the number of the hospitalization after implantation due to HF, arrhythmias, shock, the percentage of biventricular pacing (loss of CRT, the dislocation of the lead, infection, arrhythmias, and high thresholds), the kind of CRT (CRT-D and CRT-P), patients' rhythm 6 months after implantation (normal sinus rhythm, atrial fibrillation, and AT), the QRS width, and the location of the coronary sinus (lateral, posterior, and anterolateral) were all recorded. The following selection criteria for CRT were applied: moderate-to-severe HF (NYHA class III or IV], LVEF=35%, and QRS duration >120 ms with a left bundle branch block configuration. Patients with a recent myocardial infarction (<3 mon) or decompensated HF were excluded.

Before pacemaker implantation, clinical status was assessed and 2D echocardiography was performed to assess LV volumes and LVEF. Next, tissue Doppler imaging was performed to evaluate LV dyssynchrony. LV dyssynchrony was reassessed immediately after implantation. Clinical status, LVEF, and LV volumes were reassessed at 6 months' follow-up.

Clinical Evaluation

The evaluation of clinical status included an assessment of the NYHA functional class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire), and the evaluation of exercise capacity using the 6-minute corridor-walk test. Patients with an improvement of at least 1 NYHA functional class at 6 months' follow-up were classified as responders. In addition, a long-term follow-up was performed by chart reviews, telephone contacts, and outpatient visits. Events were classified as death or heart transplantation. Follow-up data were acquired for up to 5 years.

Statistical Analysis

The continuous and categorical variables are presented as mean±standard deviation and percentages. The Student *t*-test was used to compare the quantitative variables, and the χ^2 test was applied to compare the categorical variables. The SPSS software, version 18.0 (Chicago, USA), was used for all the statistical analyses. The nonparametric test was employed to compare the relationship between the nonparametric variables with normal distributions and the other variables. Additionally, the nonparametric test was used to measure the NYHA functional class before and after CRT or to measure the pattern of the change. The Man–Whitney *U*-test was utilized to measure and to compare the QRT interval differences between the 2 groups.

RESULTS

Totally 229 patients were enrolled [129 (56.3%) male and 100 (43.7%) female; mean age=62.90±12.97 y, and age range=9–24]. The demographic and clinical baseline characteristics are depicted in Table 1. In the present study, hypertrophic cardiomyopathy, valvular heart disease, dilated cardiomyopathy (DCM), ICM, and ICMP were seen in 1 (5%), 1 (5%), 103 (48.4%), and 108 (50.7%) patients, respectively. According to Table 1, LVEDV, LVESV before CRT implantation, and LVEF were 179.60±73.68 mL (range=42–400), 125.58±105.86 mL (range=5.20–489), and 18.75±6.58% (range=5–35), respectively. The prevalence of the NYHA functional class before and after CRT implantation is shown in Table 2. Out of the 206 cases, 185 (88.6%) cases were alive and the most relevant causes of mortality were HF decompensation and arrhythmias: 15 (62.5%), 7 (29.2%), and 2 (8.3%), respectively. At 6 months' follow-up, normal sinus rhythms and then atrial fibrillation were seen, respectively, in 190 (88%) and 26 (12%) of the patients

Out of the 216 CRT-implanted cases, 165 (88.7%) were CRT-D and 21 cases (11.3%) were CRT-P. Out of the 222 cases with coronary sinus locations, the most relevant site was anterolateral in 71 (32%) patients and then MCV in 1 (5%) case and PLV in 1 (5%) case (Table 2). The hospitalization duration was 1.62±1.23 days (range=1–6 d).

The most frequent reasons for hospitalization in the patients were decompensation of HF, arrhythmias, and appropriate or successful and inappropriate or unsuccessful shock, which were respectively seen in 40 (69%), 2 (3.4%), 6 (10.3%), 8 (13.8%), and 2 (3.4%) patients. The

QRS mean width was 21.10±148.60 ms (range=100–200).

Eighty-four (68.1%) female patients had DCM, whereas 39 (3.8%) men had DCM. Moreover, 30 (31.9%) of the women had ICMP, while 78 (65.5%) of the men had ICMP. The alterations in the NYHA functional class before and after CRT were measured, and no significant association was found (0.4% and 0.9%, respectively, *P*<0.05).

Regarding the association between sex and the NYHA classification before CRT implantation, the result revealed that out of the 73 women and the 80 men, 2 (2.7%) females and 6 (7.5%) males had the NYHA functional class I and 53 (72.6%) of the females and 48 (60%) of the males had the NYHA functional class II. Sixteen (21.9%) of the females had functional class III, while 24 (30%) of the males had functional class III . Two (2.8%) of the women and 2 (2.5%) of the men were found to have functional class IV; however, no significant association was found between the males and the females regarding the NYHA functional class (*P*=0.4).

DCM was mostly seen in the females, while ICMP was predominantly seen in the males.

In 64 (68.1%) of the females, DCM; and in 78 (65.6%) of the men, ICMP was seen.

Before CRT implantation, 53 (72.6), of the women and 48 (60%) of the men had the NYHA classification II, while 16 (21.9%) of the women and 24 (30%) of the men were found to have the NYHA functional class III; no relationship was found between the 2 groups regarding the NYHA functional class (*P*=0.4.)

The mean (SD) LVEDV in the men and the women was, respectively, 181.20±75.87 and 177.29+71.55 mL; nonetheless, no significant association between the 2 groups regarding LVEDV was seen (*P*=0.4). LVEF before CRT implantation in the men and the women was 17.73±6.31% and 20.05±6.71%, respectively, and the difference between the 2 groups regarding LVEF was significant (*P*=0.01) (Table 3).

At 6 months' follow-up, the mean (SD) LVEF in the men and the women was 18.56±6.18 and 20.78±8.96, correspondingly. No significant association between the 2 groups regarding LVEF at 6 months' follow-up was found (*P*=0.1). Biventricular pacing in the men and the women was 92.07±10.58 and 92.97±10.58; nonetheless, no significant association between the 2 groups concerning biventricular pacing was found (*P*=0.4) (Table 3). The mean age between the men and the women was measured, and it showed no significant difference between the 2 groups [men=62.13±14.26 vs women=63.89±11.12; (*P*=0.3)].

There was no significant association between sex and hospitalization (*P*=0.09); in most of the cases, the reason for hospitalization was the presence of comorbidities other than inappropriate or appropriate shock.

There was no significant association between the mortality rate and sex (*P*=0.4). Most of the deaths were seen in the males (18 [15.3%]), although the result was not statistically significant (*P*=0.05). Eighty-three (93.4%) of the women were alive. The differences of the QRS interval after CRT implantation in the men and the women were, respectively, 23.09±147.50 ms and 18.45±145 ms and the difference between the 2 groups regarding the QRS width was significant (*P*=0.001). There was no significant difference vis-à-vis the mean (SD) of LVEF before and after CRT implantation between the male and female patients (0.60±5.15 vs 0.26±6.03; *P*=0.7). Ninety (91.8%) women and 75 (85.2%) men had CRT-D, which showed that the most frequent kind of CRT implanted was CRT-D, although statistically no significant difference was found (*P*=0.08).

DISCUSSION

A previous study evaluated 137 men and 36 women with HF after the implantation of CRT and showed significantly improved echocardiographic parameters in both groups at

2 years' follow-up. The response to CRT in both men and women was similar, and no significant difference was seen regarding sex in response to CRT and long-term survival.[15]

In the MADIT CRT study, the response to CRT was improved in women in contrast to men.[16] In another study on 212 patients with HF, NICMP, and left bundle branch block, the response to CRT at 2 years' follow-up was 71%, which was higher in women than in men (84% vs 58%). In addition, the response to CRT when the QRS width was smaller was higher in men. (When the QRS width was <150 ms, a response of 86% vs 36% was expected; and the QRS width was >150 ms, this rate was expected to be 83% vs 69%).[17]

After CRT implantation, the 1-year survival rate was 91%, the 5-year survival rate was 63%, and the 10-year survival rate was 39%; however, total death in women in comparison to men was low. The female gender was defined as the independent predictor factor for the total mortality rate.[18]

Our study confirmed that there is a significant association between sex and LVEF (*P*<0.05). The mortality rate was greater in our male patients than in our female patients (*P*<0.05). LVEF alterations between the 2 groups were nearly the same (*P*>0.05).

We detected DCM in 68.1% of the female and ICMP in 65.6% of the male patients. Additionally, 31.9% of the females had ICMP, while 65.5% of the men had ICMP (*P*<0.001).

According to a substudy from the MADIT-CRT trial, women accounted for 25% of the study population. While the men received significant benefits from CRT-D therapy, the women had significantly better consequences with CRT-D therapy than the men for death or HF, for HF only, and for death at any time. The women had a significant (72%) reduction in all-cause mortality in the total population, with even larger diminutions in mortality for those with QRS=150 ms.[15]

In a European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial involving 162 patients with the NYHA functional class I and II and HF, LVEF was 0.35 and QRS was 120 ms, and practically 20% of the subjects were female. In addition, the clinical composite end point of deteriorated HF was reduced to a comparable degree with CRT therapy in the women and men.[19]

According to some studies on HF, women—especially those with non-ischemic heart disease—have an overall survival advantage.[20] Research has also shown that women achieve greater reductions in left conduction disturbances and greater cardiac dyssynchrony than men, which might explain why women were more responsive to CRT than men in our investigation.

It is commonly believed that in subjects without heart disease, women have—on average— QRS durations that are approximately 10 ms shorter than those in men.[21] Overall, in subjects with HF, a prolongation of QRS=120 ms occurs in 14% to 47% of patients.[22] In the MADIT-CRT trial, for any given QRS duration=130 ms, women might have—on a relative basis—more conduction disturbances and greater cardiac dyssynchrony than men, and this might clarify why women were more responsive to CRT than men in those trials.[15]

Likewise, in our investigation, the mean of the QRS width after CRT implantation in the men was approximately more than the QRS width in the women (147.50±23.09 vs 145±18.45; *P*=0.001).

In the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, women made up 33% of the study population. These female patients had a 56% reduction in the risk of sudden cardiac death with CRT-D compared with optimal pharmacologic therapy, and the female sex was associated with reduced risks in conjunction with CRT-D therapy.[23]

The results of that study are in accordance with our results, showing that most of the deaths were seen in males (15.3%), although this result was not statistically significant (*P*=0.05). Of all the female patients, 93.4% survived. The mean QRS width after CRT implantation was 147.50±23.09 in the men and 145±18.45 in the women; the difference between the 2 groups regarding the QRS width was significant (*P*=0.001).

CONCLUSIONS

Totally, the women in the present study obtained significantly greater reductions in death or HF (whichever came first), HF alone, and all-cause mortality with CRT-D therapy than did the men. This finding is most probably due to the fact that these more favorable results for women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men. At 6 months' follow-up, most of the patients had a normal sinus rhythm. Most of the deaths were seen in the males. The men had slightly greater QRS widths after CRT implantation than did their female counterparts. LVEF before and after CRT was significantly greater in the females than in the males; the difference, however, was significant before the implantation.

Table 1. Baseline characteristics of the study population

		Men (N=206)	Women	*P* value
Age (y)		62.13±14	63.89±11.04	0.3
NYHA class	I	6(7.5%)	2(2.7%)	0.4
	II	53(72.6%)	48(60%)	
	III	24(30%)	16(21.9%)	
	IV	2(2.5%)	2(2.5%)	
QRS (male, female) ms		147	145	0.4
Left ventricular ejection fraction		17.7±6.31	20±8.7	0.1
Left ventricular end-diastolic volume		181.2±75	177.29±71	0.3
Type of cardiomyopathy (male, female)	hypertrophic cardiomyopathy	1(0.8%)	0	*P*<0.001
	valvular heart disease	1(0.8%)	0	
	dilated cardiomyopathy	39(3.8%)	64(68%)	
	ischemic cardiomyopathy	78(65.5%)	30(31.9%)	

Table 2. Prevalence of the clinical data

Variables		N (percent)
Arrhythmia	normal sinus rhythm atrial fibrillation	190(88%) 26(12%)
Coronary sinus location of the lead	anterolateral	71(32%)
Reason for hospitalization	MCV	1(5%)
	PLV	1(5%)
	other reason	40(69%)
	heart failure	8(13.8%)
	appropriate shock	6(10.3)
	inappropriate shock	2(3.4%)
	arrhythmia	2(3.4%)

Table 3. LVEF alterations before and after CRT implantation

	LVEF (Females)	LVEF (Males)	*P* value
Before CRT	20.05±6.71	20.78±8.96	0.01
After CRT	17.73±6.31	18.56±6.18	0.1

CRT, Cardiac resynchronization therapy; LVEF, Left ventricular ejection fraction
P<0.05 was considered to be the level of significance.

Table 4. Patients' outcome after CRT implantation

Outcome	N(percent) Mean±SD		*P* value
CS lead location lateral	Male	51(41.5%)	0.7
	Female	46(46.5%)	
CRT-D	Male	90(91.8%)	0.08
	Female	75(85.2%)	
QRS width (ms)	Male	147.50±23.09	0.001
	Female	145±18.45	
Death	Male	18(15.3%)	0.05
	Female	83(93.4%)	
Mortality rate Other reason (%)	Male	10(55.6%)	0.4
	Female	5(83.3%)	
AF (%)	Male	6(33.3%)	
	Female	1(16.7%)	
BVP (%)	Male	92.07±10.58	0.4
	Female	92.97±10.58	

CS, Coronary sinus; CRT, Cardiac resynchronization therapy; AF, Atrial fibrillation; BVP, Biventricular pacing
P<0.05 was considered to be the level of significance.

Table 5. Clinical and demographic data comparison between the males and females

	Male/ Female		*P* value
Age (y)	Male	62.13±14.24	0.3
	female	63.89±11.12	
LVEDV (mL)	male	181.20±75.87	0.4
	female	177.29±71.55	
BVP (%)	Male	92.07±16.20	0.4
	female	92.97±10.58	
QRS (ms)	male	147.50±23.09	0.8
	female	145.51±18.45	

BVP, Biventricular pacing; LVEDV, Left ventricular end-diastolic volume
P<0.05 was considered to be the level of significance.

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