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ORIGINAL ARTICLE

Heart Size Corrected Electrical Dyssynchrony and Its Impact on Sex-Specific Response to Cardiac Resynchronization Therapy

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BACKGROUND: Women are less likely to receive cardiac resynchronization therapy, yet, they are more responsive to the therapy and respond at shorter QRS duration. The present study hypothesized that a relatively larger left ventricular (LV) electrical dyssynchrony in smaller hearts contributes to the better cardiac resynchronization therapy response in women. For this, the vectorcardiography-derived QRS area is used, since it allows for a more detailed quantification of electrical dyssynchrony compared with conventional electrocardiographic markers.

METHODS: Data from a multicenter registry of 725 cardiac resynchronization therapy patients (median follow-up, 4.2 years [interquartile range, 2.7–6.1]) were analyzed. Baseline electrical dyssynchrony was evaluated using the QRS area and the corrected QRS area for heart size using the LV end-diastolic volume (QRSarea/LVEDV). Impact of the QRSarea/LVEDV ratio on the association between sex and LV reverse remodeling (LV end-systolic volume change) and sex and the composite outcome of all-cause mortality, LV assist device implantation, or heart transplantation was assessed.

RESULTS: At baseline, women (n=228) displayed larger electrical dyssynchrony than men (QRS area, 132±55 versus 123±58 µVs; *P*=0.043), which was even more pronounced for the QRSarea/LVEDV ratio (0.76±0.46 versus 0.57±0.34 µVs/mL; *P*<0.001). After multivariable analyses, female sex was associated with LV end-systolic volume change (β=0.12; *P*=0.003) and a lower occurrence of the composite outcome (hazard ratio, 0.59 [0.42–0.85]; *P*=0.004). A part of the female advantage regarding reverse remodeling was attributed to the larger QRSarea/LVEDV ratio in women (25-fold change in β from 0.12 to 0.09). The larger QRSarea/LVEDV ratio did not contribute to the better survival observed in women. In both volumetric responders and nonresponders, female sex remained strongly associated with a lower risk of the composite outcome (adjusted hazard ratio, 0.59 [0.36–0.97]; *P*=0.036; and 0.55 [0.33–0.90]; *P*=0.018, respectively).

CONCLUSIONS: Greater electrical dyssynchrony in smaller hearts contributes, in part, to more reverse remodeling observed in women after cardiac resynchronization therapy, but this does not explain their better long-term outcomes.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiac resynchronization therapy ■ electrocardiography ■ heart failure ■ sex ■ vectorcardiography

In the past decade, it has become increasingly clear that sex differences play an important role in cardiac disease susceptibility related symptoms and the effect of treatment.[1,2] This is also true for cardiac resynchronization therapy (CRT), an effective treatment for patients with medically refractory heart failure with an ejection fraction ≤35% and a prolonged QRS duration (QRSd). Various clinical trials assessing the effect

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WHAT IS KNOWN?

- Women respond better to cardiac resynchronization therapy, yet are less likely to be treated with cardiac resynchronization therapy.
- Because female hearts are smaller, they may experience on a relative basis greater electrical dyssynchrony.
- The extent of electrical dyssynchrony is, in part, reflected by the QRS duration but may be better quantified with the vectorcardiographic QRS area.

WHAT THE STUDY ADDS?

- Female cardiac resynchronization therapy recipients display more electrical dyssynchrony at baseline compared with their male counterparts, which is most pronounced when correcting electrical dyssynchrony for heart size using the QRS area/left ventricular end-diastolic volume ratio.
- A larger QRS area for heart size using the left ventricular end-diastolic volume ratio, in part, contributes to the greater amount of left ventricular reverse remodeling observed in women after cardiac resynchronization therapy but not to their better long-term outcomes.

Nonstandard Abbreviations and Acronyms

ΔLVESV	left ventricular end-systolic volume change
CRT	cardiac resynchronization therapy
HR	hazard ratio
LBBB	left bundle branch block
LVEDV	left ventricular end-diastolic volume
LV	left ventricle
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy
QRSarea/LVEDV	QRS area for heart size using the LV end-diastolic volume
QRSd	QRS duration

of sex-specific response to CRT showed that women more often demonstrate reverse remodeling and experience improved survival after CRT.[3–7] Unfortunately, the underlying mechanisms for the improved outcomes in women remain largely unknown. Because women have an overall survival advantage over men,[8,9] it is possible that improved survival trends observed in women after CRT are related to an intrinsic survival advantage in women.[4] Yet, some studies ascribed the better outcome in women to more favorable clinical characteristics since women more frequently have a nonischemic etiology of heart failure or a typical left bundle branch block (LBBB).[3,10,11] Interesting is the notion that women generally have a shorter QRSd than men and show response to CRT at shorter QRSd.[12,13] It has been suggested that because female hearts are smaller, they may experience, on a relative basis, greater left ventricular (LV) dyssynchrony compared with male hearts at identical QRSd, hence the greater CRT benefit.[7,14] While the extent of electrical dyssynchrony is, in part, reflected by the QRSd, recent work displayed that quantification of electrical dyssynchrony may better be achieved with the vectorcardiographic QRS area.[15–18] By normalizing the QRS area for LV dimensions using the LV end-diastolic volume (LVEDV), the impact of a relatively larger electrical dyssynchrony in women can be assessed for the involvement in their better CRT outcomes. Accordingly, in the present study, we aimed to investigate whether sex-specific differences in LV reverse remodeling and long-term outcome after CRT can be attributed to normalization of QRS area for heart size using the LVEDV (QRSarea/LVEDV ratio).

METHODS

We analyzed data from the Maastricht-Utrecht-Groningen database, consisting of a total of 1946 patients (1394 men and 552 women) implanted with a CRT device in 3 university hospitals in the Netherlands between 2001 and 2015.[17] Seven hundred and twenty-five patients from this cohort were included in the present study of whom 228 were women and 497 were men. Inclusion criteria were as follows: (1) all patients with a de novo CRT implantation, (2) all patients with an intrinsic QRSd of ≥120 ms and ejection fraction ≤35%, and (3) patients with available digital 12-lead ECG and echocardiogram at baseline and follow-up (Figure 1). Finally, patients with atrial fibrillation were excluded from the analysis due to its confounding nature in CRT. Optimization of CRT settings was left to the discretion of the patients' physician. The Dutch Central Committee on Human-Related Research allows the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used were handled anonymously. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection

Patient data were retrieved from the patient records at the 3 hospitals as described before.[17] LV volumes were measured on echocardiographic images using the modified biplane Simpson method. LV dimensions were indexed for body surface area. Baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System) and were evaluated for QRSd and the presence of LBBB morphology according to the European Society of Cardiology definition (QRSd≥120 ms, QS or rS in lead V_1, broad [frequently notched or slurred] R waves in lead I, aVL, V_5, or V_6, and absent Q waves in leads V_5 and V_6).[19] Vectorcardiographic QRS area was

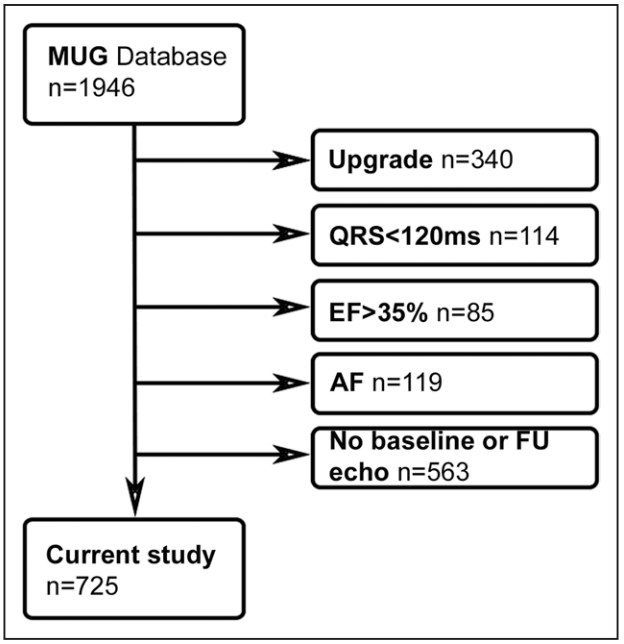

Figure 1. Patient data collection and availability for analyses. Selection process of patients included in the present analyses. AF indicates atrial fibrillation; echo, echocardiography; EF, ejection fraction; FU, follow-up; and MUG, Maastricht-Utrecht-Groningen.

calculated with custom-made Matlab software (MathWorks, Inc, Natick, MA). ECGs were converted using the Kors conversion matrix into the 3 orthogonal vectorcardiography leads (X, Y, and Z matrix; Figure 2).[20] QRS area was subsequently calculated as the sum of the area under the QRS complex in the orthogonal vectorcardiographic leads (QRS area=[QRS area,x^2+QRSarea,y^2+QRSarea,z^2]$^{1/2}$). The QRS area was corrected for the echocardiographic LVEDV to correct for heart size (QRSarea/LVEDV).

Study Outcomes

LV reverse remodeling after CRT was determined by comparing baseline and 6- to 12-month follow-up echocardiographic LV end-systolic volume change (ΔLVESV). Patients with an LV end-systolic volume decrease of ≥15% at follow-up echocardiography were considered volumetric responders. The composite outcome of all-cause mortality, LV assist device implantation, and cardiac transplantation was assessed based on patient' records.

Statistical Analysis

All statistical tests were performed in SPSS, version 25 (IBM, Armonk, NY). Continuous data were expressed using mean (SD) or median (interquartile range), depending on the normality of data. Categorical data were described by an absolute number of occurrences and associated frequency (%). Differences between groups were assessed using a *t* test or Mann-Whitney *U* test, dependent on normality of the data. Pearson χ^2 tests were used for dichotomous variables. To test the association between sex and ΔLVESV and sex and the composite outcome, univariable and multivariable linear and Cox regression analyses were performed for which β and hazard ratios (HRs) were reported, respectively. Multivariable regression analyses were performed with adjustment for potential confounders. Confounders were selected based on baseline differences between women and men and covariates that were univariately (P<0.1) associated with either ΔLVESV or the composite outcome. Correlation tests were performed to test for multicollinearity. Covariates with signs of multicollinearity (Pearson r>0.8; P<0.05 or a variance inflation factor >10) were excluded from the model. To determine the impact of the QRSarea/LVEDV ratio on the association between sex and CRT response, the multivariable models were run with and without correction for the QRS area and QRSarea/LVEDV ratio separately. A change in estimate criterion (β or HR) of ≥10%

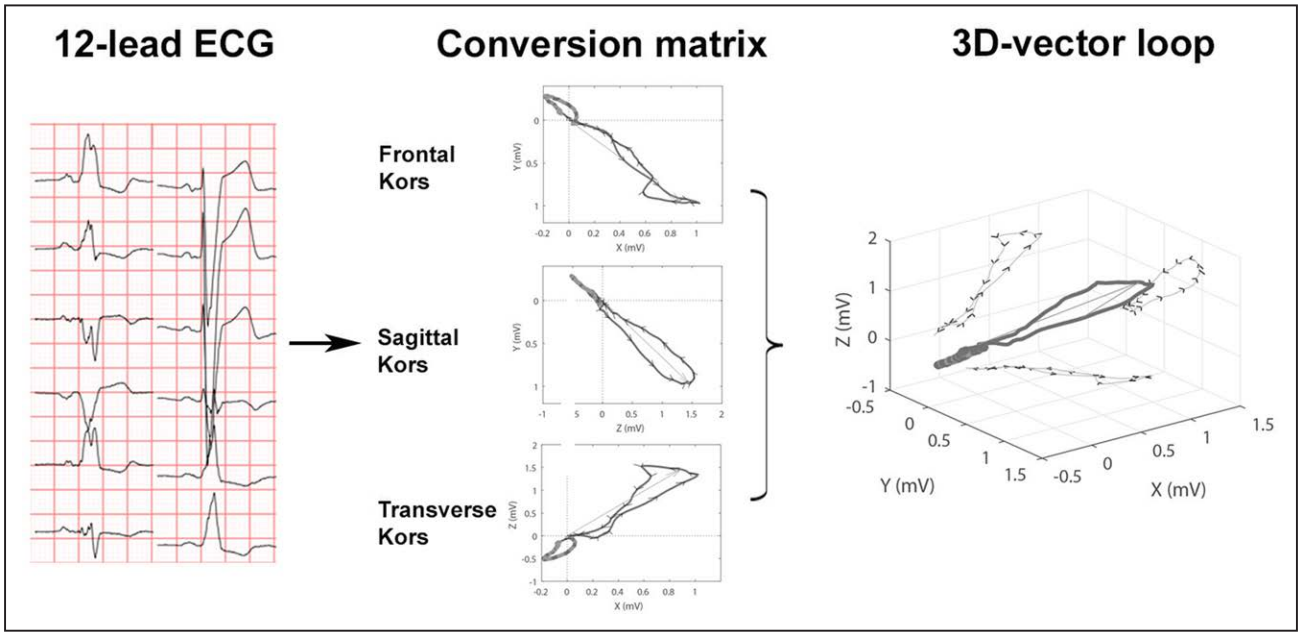

Figure 2. Conversion of 12-lead ECG to vectorcardiogram. Conversion of 12-lead ECG by the Kors conversion matrix into the three orthogonal vectorcardiography lead matrix and a 3-dimensional (3D) vector loop. QRS area is calculated as the area of the vector loop.

was used to determine whether the QRSarea/LVEDV ratio impacts on the association between sex and CRT response. Assumptions of the Cox model were tested by visual assessment of log-minus-log plots. Assumptions of multivariable linear regression were checked for nonlinearity and heteroskedasticity by graphical analyses. Normality of residuals was visually examined by a Q-Q plot. Missing data were handled by a 5-fold multiple imputation to prevent incomplete case analysis in the multivariable model. Of the variables considered in the multivariable modeling, only 3 variables had missing data (<5% missing at random by Little Missing Completely At Random test >0.05). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

The baseline characteristics are displayed in Table 1. Women (31.4% of the study population) displayed less ischemic cardiomyopathy (28.5% versus 58.8%; $P<0.001$) and more LBBB (88.2% versus 77.9%; $P=0.001$). QRSd was shorter (159±19 versus 164±21 ms; $P=0.002$) while QRS area was larger in women (132±55 versus 123±58 µVs; $P=0.043$). Moreover, LV volumes were smaller in women (LVEDV, 183 [143–235] versus 230 [176–295] mL; $P<0.001$). Consequently, the QRSarea/LVEDV ratio was profoundly larger in women compared with men (0.76±0.46 versus 0.57±0.35 µVs/mL; $P<0.001$; Figure 3). The differences in baseline characteristics for volumetric CRT response and the secondary end point are provided in Tables I and II in the Data Supplement.

LV Reverse Remodeling

Median follow-up time was 6.2 months (5.7–6.8). Women were more often volumetric responder (68.4% versus 52.5%; $P<0.001$) and showed more reverse remodeling (ΔLVESV, −27±30% versus −17±30%; $P<0.001$). Women displayed more LV end-systolic volume reduction than men for any QRSarea/LVEDV ratio <1, while at a ratio >1 there seemed to be no benefit of women over men (Figure 4). In univariable linear regression analysis, female sex was strongly associated with ΔLVESV ($\beta=0.193$; $P<0.001$). After adjusting for possible confounders (ischemic cardiomyopathy, device type, statin use, indexed LVEDV, LBBB morphology, QRSd, and PR interval), female sex remained significantly associated with volumetric CRT response ($\beta=0.12$; $P=0.003$; Table 2, model 1). To investigate the impact of a relatively larger electrical dyssynchrony in smaller hearts, the QRS area and the QRSarea/LVEDV ratio were added separately to the multivariable model. The adjusted β of female sex on volumetric CRT response changed from 0.12 to 0.09 (25% change) with the addition of the QRSarea/LVEDV ratio (Table 2). This suggests that the QRSarea/LVEDV ratio impacts on the association between female sex and ΔLVESV and, therefore, in part, contributes to the greater amount of LV reverse remodeling observed in female patients. Of note, Table III in the Data Supplement displays the full univariable and multivariable model.

Table 1. Baseline Characteristics of Study Population

	Women, n=228 (31.4)	Men, n=497 (68.6)	*P* value
Age, y	64.7±11.0	65.6±10.1	0.279
Body mass index, kg/m²	26.8±5.7	26.6±4.3	0.631
NYHA functional class, n (%)			
III/IV	160 (70.2)	292 (58.8)	0.003
CRT-D	214 (93.9)	482 (97.0)	0.046
Comorbidities, n (%)			
Ischemic cardiomyopathy	65 (28.5)	292 (58.8)	<0.001
Diabetes	50 (22.0)	115 (23.1)	0.741
Hypertension	91 (40.3)	214 (43.1)	0.468
Glomerular filtration rate, mL/min	68±31	75±32	0.009
Medication, n (%)			
β-Blocker	196 (86.0)	424 (85.3)	0.817
ACE inhibitor/ARB	209 (91.7)	456 (91.8)	0.970
Diuretics	187 (82.0)	397 (79.9)	0.499
Statin	101 (44.3)	321 (64.6)	<0.001
Antiarrhythmics*	13 (5.7)	62 (12.5)	0.005
Echocardiography			
LV ejection fraction, %	23.0±7.5	22.8±6.9	0.691
LVESVi, mL/m²	75 (57–105)	87 (67–114)	<0.001
LVEDVi, mL/m²	99 (79–131)	114 (89–146)	<0.001
Electrocardiography			
LBBB, n (%)	201 (88.2)	387 (77.9)	0.001
QRS duration, ms	158.8±18.9	163.9±21.4	0.002
PR interval, ms	178±30	195±40	<0.001
Heart rate, bpm	74.3±14.6	80.8±14.0	0.002
Vectorcardiography			
QRS area, µVs	131.8±55.3	122.5±57.9	0.043
Correction for heart size			
QRS area/LVEDV, µVs/mL	0.76±0.46	0.57±0.35	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy defibrillator; LBBB, left bundle branch block; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; and NYHA, New York Heart Association.

*Amiodarone/verapamil/flecainide/sotalol.

All-Cause Mortality, LVAD Implant, or Cardiac Transplantation

Over a median follow-up time of 4.2 (interquartile range, 2.7–6.1) years, 231 patients (31.9%) reached the composite outcome of whom 54 (23.4%) were women and 177 (76.6%) were men ($P=0.001$). Median time to the composite outcome was significantly longer in women (4.7 [interquartile range, 3.1–6.6] versus 3.9 [interquartile range, 2.4–5.8] years; $P=0.004$). No patients in the study cohort were lost to follow-up. In univariable Cox regression

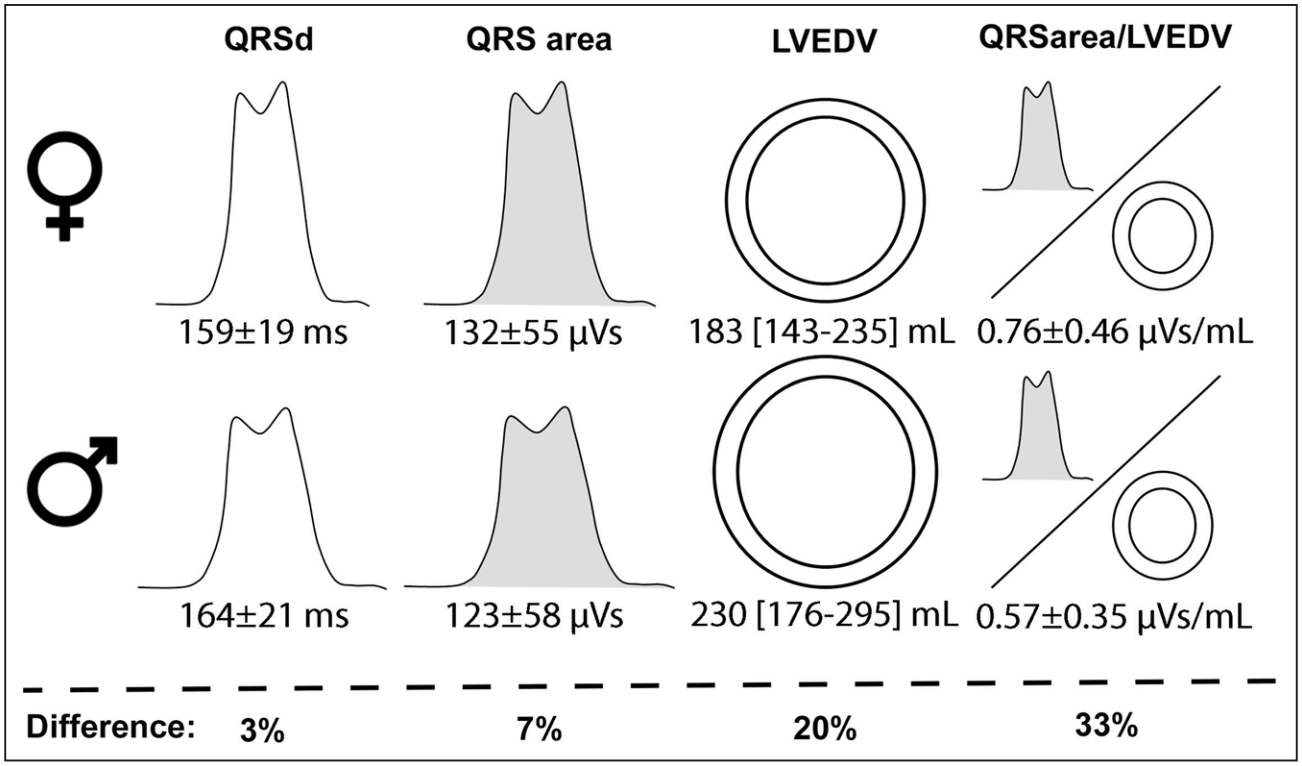

Figure 3. Sex differences in left ventricular (LV) dimensions and LV dyssynchrony.
Group mean values for electrical dyssynchrony, heart size, and heart size corrected electrical dyssynchrony are displayed for both sexes. Despite an overall shorter QRS duration (QRSd) in female cardiac resynchronization therapy recipients, dyssynchrony was considerably greater in women. LVEDV indicates left ventricular end-diastolic volume.

analysis, female sex was associated with a more favorable survival free of the composite outcome (HR, 0.56 [0.41–0.76]; $P<0.001$). After adjusting for possible confounders (age, New York Heart Association class, ischemic cardiomyopathy, kidney function, antiarrhythmic use, indexed LVEDV, LBBB morphology, QRSd, and PR interval), female sex remained strongly associated with the composite outcome (HR, 0.59 [0.42–0.85]; $P=0.004$). Adding QRSarea/LVEDV to the multivariable model changed the HR of female sex from 0.59 to 0.62 (5.1% change), suggesting that the larger QRSarea/LVEDV ratio in women does not contribute to their better long-term outcomes (Table 3; Figure 5). Of note, Table IV in the Data Supplement displays the full univariable and multivariable Cox regression analysis.

Finally, to assess the impact of sex disparities in volumetric response to CRT on the occurrence of the composite outcome, adjusted event curves for both sexes were specified separately for volumetric responders and nonresponders in Figure 6. Among both CRT responders and nonresponders, female sex remained strongly associated with the composite end point (HR, 0.60 [0.37–0.99]; $P=0.040$ and HR, 0.56 [0.34–0.92]; $P=0.023$, respectively).

DISCUSSION

In this multicenter cohort, we investigated to which extent sex differences in heart size corrected electrical dyssynchrony at baseline can explain the repeatedly observed better outcomes in women. Electrical dyssynchrony was quantified by measuring the QRS area, which was adjusted for heart size using the QRSarea/LVEDV ratio. Our main findings were that (1) women have a larger QRS area than men and an even more pronouncedly larger QRSarea/LVEDV ratio, (2) this larger QRSarea/LVEDV contributes, in part, to the greater LV end-systolic volume reduction in women after CRT, still (3) the superior outcome and survival in female CRT recipients is not explained by the larger QRSarea/LVEDV ratio nor their greater volumetric response after CRT.

Superior Long-Term Survival in Female CRT Recipients

The observation of better outcomes in women after CRT has led to controversies about a potential sex-specific response. While some studies ascribed the better outcome in women to baseline differences,[10,21] others implied that the better outcomes in women are intrinsic to female sex.[5,22,23] Surprising is that numerous studies failed to provide data on QRS morphology,[21–23] an important confounder in the sex-CRT response relationship, because women more often show a typical LBBB at baseline.[24,25] Still, several studies to date have displayed that even among exclusively LBBB patients, women do better than men and that the

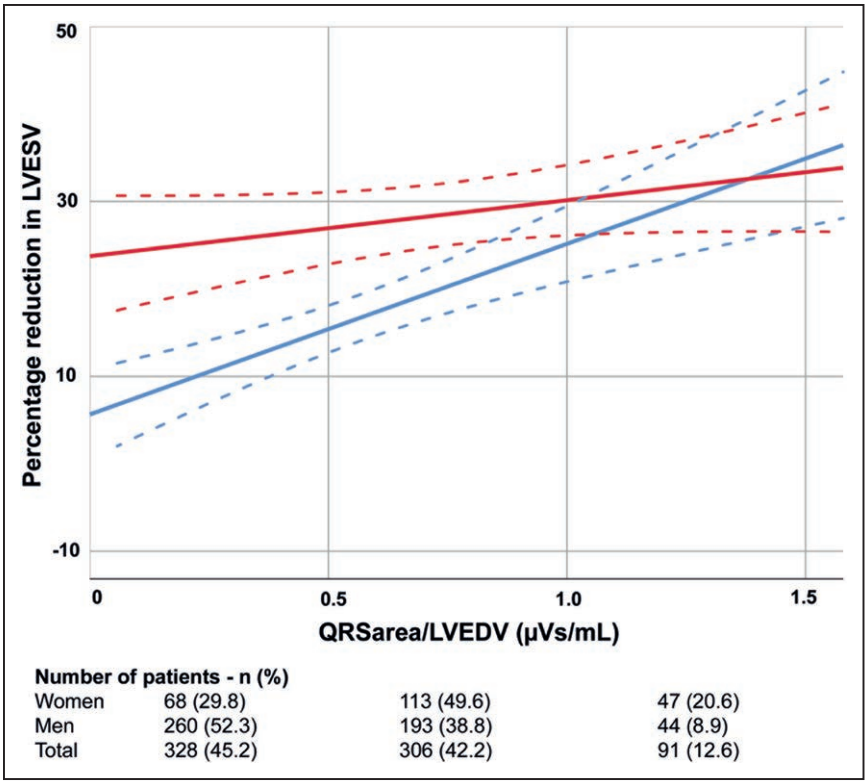

Figure 4. Left ventricular reverse remodeling according to QRS area for heart size using the left ventricular end-diastolic volume (QRSarea/LVEDV) as continuum. The mean amount of left ventricular end-systolic volume (LVESV) reduction is displayed for any value of QRSarea/LVEDV with corresponding 95% CIs. In both sexes, greater QRSarea/LVEDV ratios at baseline yield greater LVESV change (ΔLVESV) at follow-up. At the lower QRSarea/LVEDV values, women (red) show more ΔLVESV compared with men (blue), but there is no evident benefit of women over men in terms of reverse remodeling in patients with a QRSarea/LVEDV ratio >1.0.

superior outcome in women is not explained by the application of strict LBBB criteria.[3,7,24] The same seems true for heart failure etiology. While women less often experience ischemic heart failure, a subanalysis of the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) demonstrated that among CRT patients with nonischemic heart failure, women do better than men.[3] Another factor that might contribute to the improved event-free survival in female CRT recipients is that women experience more reverse remodeling after CRT.[4,6] Leyva et al,[5] however, demonstrated in a large cohort study of 550 patients undergoing CRT that the superior long-term survival in women was not explained by their greater volumetric response to CRT. These aforementioned findings are in line with the results of the present study and imply that it is not the greater volumetric response nor a more favorable underlying substrate (eg, LBBB or ischemic cardiomyopathy) in women that explains their superior event-free survival.

Heart Size Corrected LV Dyssynchrony and CRT Response

The notion that women may have greater LV dyssynchrony than men is not new.[3,7,14,26] Two large patient cohort studies displayed that female CRT recipients more frequently show mechanical dyssynchrony on 2-dimensional echocardiography than their male counterparts.[10,26] Moreover, because women have smaller hearts, any single QRSd may represent greater retardation of myocardial conduction. Women may, therefore, experience on a relative basis even greater dyssynchrony than men do, which may account for their better response to CRT. This hypothesis has been supported by 2 previous studies that corrected the QRSd for

Table 2. Multivariable Regression Models of Association of Female Sex With ΔLVESV at Follow-Up

Multivariable linear regression model	β (Standardized)	*P* value	Fold change, %
Model 1*			
Adjusted β of association between female sex and ΔLVESV	0.12	0.003	
Model 1*+QRS area			
Adjusted β of association between female sex and ΔLVESV	0.11	0.004	8.3
Model 1*+QRSarea/LVEDV ratio			
Adjusted β of association between female sex and ΔLVESV	0.09	0.023	25

β: standardized regression coefficient (represents the number of SDs that the outcome will change as a result of 1 SD change in the predictor). Fold change reported with respect to model 1. LBBB indicates left bundle branch block; LVEDV, left ventricular end-diastolic volume; and (Δ)LVESV, (change in) left ventricular end-systolic volume.

*Covariates in model 1: device type, ischemic heart failure, statin use, indexed LVEDV, LBBB morphology, QRS duration, and PR interval.

Table 3. Multivariable Regression Models of Association of Female Sex With All-Cause Mortality, Left Ventricular Assist Device Implant, or Heart Transplant

Multivariable Cox regression model	HR (95% CI)	*P* value	Fold change, %
Model 2*			
Adjusted HR of association between female sex and the secondary end point	0.59 (0.42–0.85)	0.004	
Model 2*+QRS area			
Adjusted HR of association between female sex and the secondary end point	0.60 (0.42–0.86)	0.005	1.7
Model 2*+QRSarea/LVEDV ratio			
Adjusted HR of association between female sex and the secondary end point	0.62 (0.44–0.89)	0.009	5.1

HR indicates hazard ratio; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEDVi, indexed left ventricular end-diastolic volume; and NYHA, New York Heart Association.

*Covariates in model 2: age, NYHA class, ischemic heart failure, kidney function, antiarrhythmics use, LVEDVi, LBBB morphology, QRS duration, PR interval, and QRS area. Fold change reported with respect to model 2.

LV dimensions. Varma et al[7] demonstrated in 130 patients that sex differences in volumetric CRT response resolved by normalization of the QRSd for heart size using LV mass or volumes. In addition to these findings, Zweerink et al[14] suggested that a higher QRS/LVEDV ratio in women might explain their better long-term survival. This hypothesis, however, should be interpreted with caution because the study was not designed to investigate sex-based differences in CRT outcomes and because the authors failed to index LVEDV to BSA or transform serum creatinine values to kidney function. This is essential for a meaningful comparison between men and women since lower serum creatinine and smaller LVEDV are both traits of the female sex. Still, the assumption that it might be size, rather than sex, which is, in part, responsible for the greater CRT benefit in women is intriguing. In the present study, women displayed larger QRSarea/LVEDV ratios than men. Importantly, for any QRSarea/LVEDV ratio <1, women showed more reverse remodeling; yet, in patients with a QRSarea/LVEDV ratio >1, there was no benefit of women over men. While these patients only accounted for 12.6% of the study population, this is an important finding suggesting that among patients with the most favorable underlying electrical substrate, both sexes benefit equally from CRT. In this respect, this study is the first to expose sex-specific differences in CRT outcomes by quantifying the electrical substrate amendable by CRT with the vectorcardiography-derived QRS area.

Greater Dyssynchrony: Trait of the Female Sex or the Result of Current Patient Selection Criteria

It is imperative to realize that the interplay between sex, LV dyssynchrony, and heart size is complex and that it

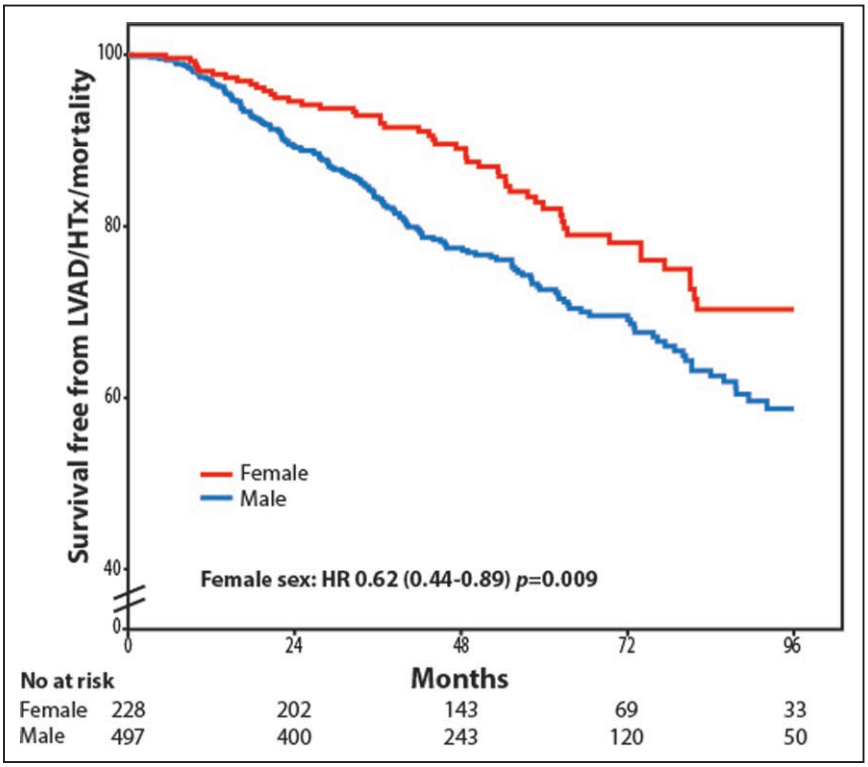

Figure 5. Adjusted event curves for association between female sex and the composite end point.
Adjusted* event curves for association between female sex and survival free from the composite end point using a Cox proportional-hazards model. A significant survival benefit of women over men is displayed. HR indicates hazard ratio; HTx, heart transplant; and LVAD, left ventricular assist device. *Adjusted for age, New York Heart Association class, ischemic cardiomyopathy, kidney function, antiarrhythmic use, indexed left ventricular end-diastolic volume, left bundle branch morphology, QRS duration, PR interval, and QRS area/left ventricular end-diastolic volume.

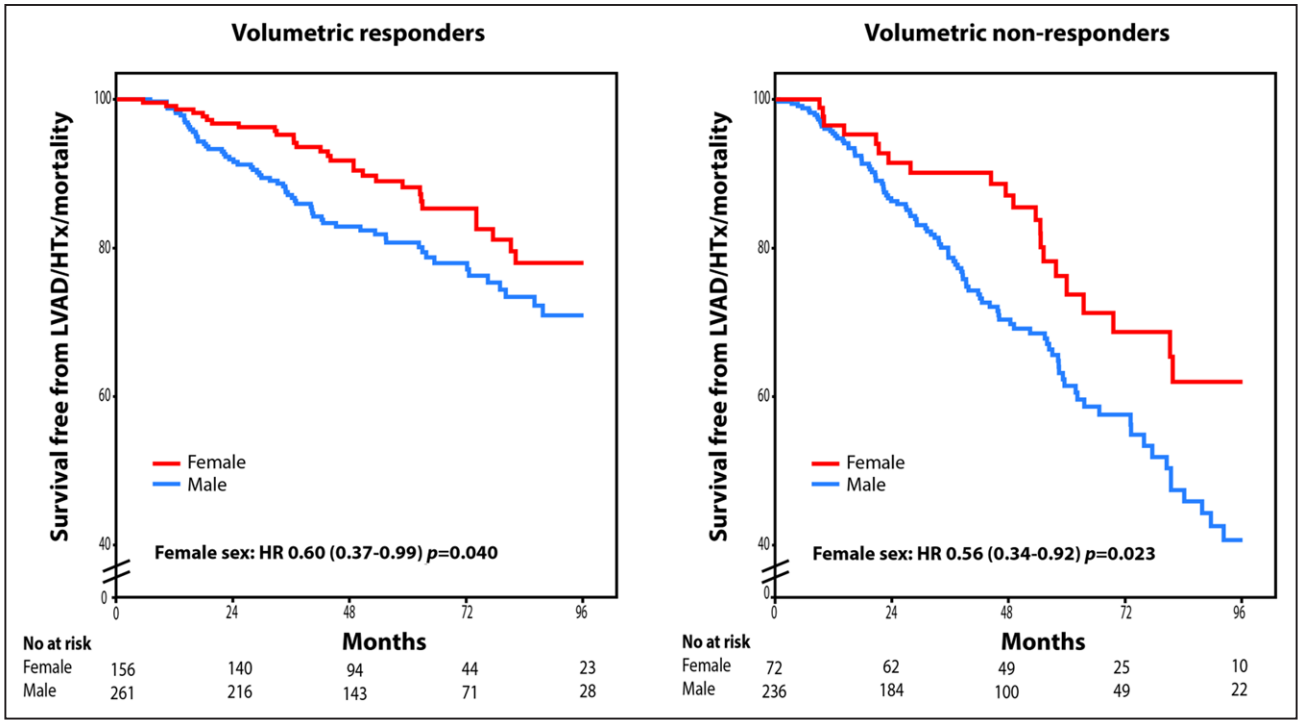

Figure 6. Adjusted event curves specified by volumetric response for the association between female sex and the composite end point.

Adjusted event curves for association between female sex and survival free from the composite end point using a Cox proportional-hazards model. A significant survival benefit of women over men is observed in both volumetric cardiac resynchronization therapy responders and nonresponders. HR indicates hazard ratio; HTx, heart transplant; and LVAD, left ventricular assist device.

remains uncertain whether potential modifying factors of sex are masking the effect of LV dyssynchrony or heart size on CRT response or vice versa. Furthermore, it should be acknowledged that the larger QRSarea/LVEDV ratio could, by itself, be a trait of the female sex but could, on the other hand, also be independent of female sex and a consequence of using the same selection criteria of QRS ≥130 ms (preferably ≥150 ms) for both sexes in current CRT guidelines. The latter might lead to a selection and treatment of female patients with a relatively greater LV dyssynchrony because women, on average, have smaller hearts. Because current CRT guideline recommendations are based on clinical trials that included ~75% men, they are biased to reflect CRT outcomes in men.[4] Consequently, the use of a uniform QRSd threshold for recommending CRT in both sexes, although appropriate in men, may deny a potentially beneficial therapy to many women with a smaller QRSd but likely to benefit from CRT. This has raised discussion for the introduction of more lenient QRSd selection criteria in women.[27]

Limitations

The observational and retrospective nature of the study should be acknowledged. Due to the retrospective character and lack of a control group, we cannot show that women respond better to CRT but rather that among CRT recipients, women do better than men. Also, it would especially be of interest to investigate cardiovascular mortality because women in the general population live longer than men. Still, for a comparison of volumetric response and outcome between sexes, it can be assumed that this design is useful and allows for hypothesis generation. In addition, some selection bias might have occurred because patients with atrial fibrillation were excluded from the current analysis. Still, we investigated numerous potential confounders in the sex-CRT response relationship. Importantly, to the best of our knowledge, this is the first study to evaluate sex-specific differences in CRT outcomes by quantifying the underlying electrical substrate responsive to CRT with the vectorcardiography-derived QRS area. The QRS area has been put forward as a better alternative to QRSd or QRS morphology to assess electrical LV dyssynchrony.[15,17,28]

Conclusions

Women undergoing CRT display more LV electrical dyssynchrony at baseline as compared with men, which is most pronounced when correcting electrical dyssynchrony for heart size by echocardiographic LVEDV. The larger electrical dyssynchrony in smaller hearts, represented by the QRSarea/LVEDV ratio, contributes, in part, to the greater amount of reverse remodeling observed

in women after CRT but not to the better long-term outcomes.

ARTICLE INFORMATION

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