Gender Difference in Coronary Sinus Anatomy and Left Ventricular Lead Pacing Parameters in Patients With Cardiac Resynchronization Therapy

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Background: Recent studies have suggested better outcomes from cardiac resynchronization therapy (CRT) in women. Gender differences in coronary sinus (CS) anatomy and left ventricular (LV) lead parameters in patients undergoing CRT, however, have not been well studied.

Methods and Results: Two hundred and twenty-three consecutive patients, undergoing CRT at the University of California in San Diego Medical Center from 2003 to 2011 were included in this study. The location of the LV lead was assessed on coronary venography and chest X-ray recorded at the time of device implantation. Optimal LV lead position was defined as either mid-lateral or posterolateral LV wall. The relationship between LV lead position (optimal or non-optimal position) and LV lead parameters at completion of implant were compared between genders. No statistically significant gender differences were noted in baseline characteristics. LV lead implantation was successful in 217 patients (97.3%). Lateral or posterolateral CS branches were unavailable in more women than men (26.3% vs. 10.8%, $P=0.011$). Women had a higher LV lead pacing threshold than men ($P=0.003$) and gender was an independent risk factor of high LV lead pacing threshold ($P=0.008$).

Conclusions: Women had an anatomical disadvantage for LV lead placement and had higher LV lead pacing threshold compared to men. Implanting physicians should be aware of gender differences during LV lead placement in order to maximize CRT benefits. (*Circ J* 2013; **77**: 1424–1429)

Key Words: Biventricular pacing; Coronary sinus vein; Gender; Left ventricular lead position; Pacing threshold

Heart failure (HF) is a chronic progressive disease associated with substantial morbidity and mortality.¹ It is estimated that approximately 5 million people in the USA have HF, and hospitalizations due to HF have increased drastically over the previous 20 years.² Evidence from randomized controlled trials demonstrates that cardiac resynchronization therapy (CRT) combined with medical therapy significantly reduces morbidity and mortality in HF patients with reduced left ventricular ejection fraction (LVEF) and prolonged QRS duration.^{3–7} Several large trials have demonstrated that CRT improves symptoms of HF, quality of life, exercise capacity,^{8–11} and LV function,¹² when used in patients with New York Heart Association (NYHA) functional class III or ambulatory class IV HF, with a wide QRS complex.

Some studies have shown that women have a better response than men with regards to overall mortality, hospitalization due to HF,¹³ sudden cardiac death, appropriate ICD shock,¹⁴ and

progressive LV enlargement.¹⁵ More recently, 2 large prospective observational studies have shown that female gender is a predictive factor for survival from cardiovascular death, death from any cause, and HF hospitalizations.^{16,17} Despite this apparent better prognosis, a smaller percentage of female patients have undergone CRT compared to male patients.^{7,18} The reason(s) why female gender is associated with a better prognosis in patients with congestive HF also remains unclear.

The success of CRT largely depends on the presence, suitability, and accessibility of coronary sinus (CS) branches during implantation. Despite attempts to place LV leads in an optimal position, phrenic nerve stimulation and high LV pacing thresholds often cause difficulties, resulting in the need to reposition the LV lead in a less than optimal position, such as more proximally within the same CS branch, in a different sub-branch or in a totally different branch.¹⁹ Although anatomical differences of CS anatomy have previously been re-

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Figure 1. Angiographic classification of left ventricular (LV) lead position. (**Left**) The right anterior oblique (RAO) 30° view represents the long axis of the heart. Based on this view, the heart was divided into basal, mid-ventricular (mid), and apical segments. (**Right**) The left anterior oblique (LAO) 45° view was used to divide the LV wall along the short axis of the heart into 5 equal parts: anterior, anterolateral, lateral, posterolateral, and posterior.

ported in patients undergoing CRT,²⁰ it remains unclear whether significant anatomical differences exist between men and women and, if so, whether this has an impact on LV lead placement and LV lead parameters. Thus, the aim of this study was to investigate potential gender difference in CS anatomy and LV lead parameters among patients undergoing CRT.

Methods

We retrospectively analyzed 223 consecutive patients who underwent CRT from 2003 to 2011 at the University of California in San Diego Medical Center. Patients were referred for CRT based on current guidelines²¹ including advanced symptoms of HF (NYHA functional class II, III or IV), LVEF $\leq 35\%$, and a wide QRS complex (≥ 120 ms). Patients with a recent myocardial infarction or revascularization within 3 months were excluded. The cause of HF was considered ischemic if there was underlying significant coronary artery disease ($>50\%$ stenosis in 1 or more major coronary arteries) and/or a history of myocardial infarction or previous revascularization. All patients underwent a thorough history and physical examination, 12-lead electrocardiogram, and transthoracic echocardiogram. Each patient's medication history was carefully reviewed to ensure use of optimal medical therapy with a β -blocker and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretics, aspirin, and statins, where appropriate. All patients provided written informed consent before the procedure.

Device Implantation

Devices and leads were implanted using standard techniques.²² A coronary venous angiogram was performed before LV lead placement in at least 2 orthogonal views (right anterior oblique [RAO], 30°; and left anterior oblique [LAO], 45°). Post-implantation fluoroscopic images were obtained and stored in the same views. Final lead position was determined on biplanar fluoroscopy (in RAO and LAO views). The LV epicardial

surface was divided into 15 different segments using both RAO and LAO views.^{23–25} The RAO view was used to define the location of the LV lead along the long axis of the heart, divided into basal-ventricular, mid-ventricular and apical-ventricular segments (Figure 1).²⁶ The LAO view was used to define the location of the LV lead on the short axis: anterior, anterolateral, lateral, posterolateral, and posterior (Figure 1).²⁵ On the day after device implantation, a standard posteroanterior and lateral chest X-ray was performed in all patients. A lateral or posterolateral position on the LV wall, midway between base and apex, was most often targeted, although the final position was guided by the CS anatomy and the ability to obtain satisfactory pacing thresholds without phrenic nerve stimulation. Anterior, anterolateral or posterior branches of the CS were used only when both lateral and posterolateral branches were not suitable for LV lead placement. The implanting physicians responsible for determining segmental LV lead position were blinded to the outcome data. The devices implanted were manufactured by Medtronic (Minneapolis, MN, USA), St. Jude Medical (St. Paul, MN, USA), Boston Scientific (Indianapolis, IN, USA) or Biotronik (Berlin, Germany).

Management of LV Pacing Threshold

Pacing threshold was tested at 0.5 ms pulse width. A high LV pacing threshold was defined as >2.5 V at 0.5-ms pulse width.²⁷ If a high threshold was detected during procedure or follow-up, testing of all other possible configurations was performed in order to identify the lowest capture threshold configuration.

Follow-up

Patients underwent full device interrogation during implantation, at 24 h, 1 week and 3 months after implantation. Outpatient follow-up visits occurred at 1 week, 6 months and 12 months postoperatively and then every 6 months thereafter. At each visit, clinical functional status was recorded and device interrogation was performed. Patients were followed in a multidisciplinary CRT clinic that includes providers from the elec-

Table 1. Patient Characteristics				
	All	Men	Women	P-value
n	223	185 (83.0)	38 (17.0)	
Age (years)	63.1±13.5	63.2±13.7	62.3±13.2	0.69
NYHA class				0.19
II	69	54	15	
III	144	124	20	
IV	10	7	3	
LVEF (%)	27.1±8.1	26.9±8.1	28.4±7.5	0.28
QRS duration (ms)	152±32	153±33	145±23	0.17
Comorbidity (%)				
Hypertension	136 (61.0)	115 (62.2)	21 (55.3)	0.47
Diabetes	91 (40.8)	70 (37.8)	21 (55.2)	0.06
Hemodialysis	12 (5.4)	11 (6.0)	1 (2.6)	0.69
Atrial fibrillation	78 (39.5)	68 (42.2)	10 (26.3)	0.07
Etiology of HF				0.25
Ischemic	117 (52.5)	102 (55.1)	15 (39.5)	
Non-ischemic	106 (47.5)	83 (44.9)	23 (60.5)	

Data given as mean ± SD or n (%). HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2. CS Venography and LV Lead Position				
	All	Men	Women	P-value
No. patients	223	185	38	
Inadequate size or absence of lateral and posterolateral branch	30 (13.5)	20 (10.8)	10 (26.3)	0.011
Lead position				NS
Basal anterior	12 (5.4)	9 (4.9)	3 (7.9)	
Mid-anterior	6 (2.7)	5 (2.7)	1 (2.6)	
Apical anterior	0 (0)	0 (0)	0 (0)	
Basal lateral	10 (4.5)	7 (3.8)	3 (7.9)	
Mid-lateral	160 (71.8)	133 (71.9)	27 (71.1)	
Apical lateral	10 (4.5)	10 (5.4)	0 (0)	
Basal posterior	1 (0.5)	0 (0)	1 (2.6)	
Mid-posterior	8 (3.6)	8 (4.3)	0 (0)	
Apical posterior	10 (4.5)	8 (4.3)	2 (5.3)	
Fail	6 (2.7)	5 (2.7)	1 (2.6)	

Data given as n (%). CS, coronary sinus; lateral wall, mid-anterolateral, mid-lateral or mid-posterolateral wall; LV, left ventricular.

trophysiology and HF divisions. Medical treatment was performed at the discretion of the treating physicians.

Statistical Analysis

Anterolateral, lateral, and posterolateral segments were included in the lateral wall group for statistical analysis. Multiple regression analysis was carried out to identify independent risk factors for high pacing threshold. Any factors with $P < 0.10$ on univariate analysis were included in the multiple regression analysis.

The magnitude of change in continuous variables between patients was compared using paired t-test. Paired Wilcoxon signed rank test was used as the non-parametric alternative to the paired t-tests. Categorical variables were compared using chi-square test. $P < 0.05$ was considered statistically significant. Continuous variables are expressed as mean ± SD. All statistical analysis, including interactions, was performed with version 10.0 of SAS (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the entire study cohort were typical for patients undergoing CRT and included a mean age of 63.1±13.5 years. Etiology of cardiomyopathy was ischemic in 117 patients and non-ischemic in 106 patients. Baseline LVEF was 27±8%, and baseline QRS duration was 152±32 ms. There was no statistically significant difference in baseline characteristics between men and women (Table 1).

LV Lead Position

The final LV lead tip positions are listed in Table 2. Contrast venography of CS showed inadequate size or absence of both lateral and posterolateral branches in 20 out of 185 men (10.8%) and in 10 out of 38 women (26.3%), respectively ($P = 0.011$). In 6 patients, the LV lead could not be placed successfully in any CS branch. The causes of failure were as follows: no or small target vein (3 patients), CS dissection (2 patients), and

failure to cannulate CS (1 patient). Therefore, a total of 217 patients were included in the statistical analysis of the LV lead. Even in women, the LV lead was implanted at mid-lateral LV wall (mid-anterolateral, mid-lateral or mid-posterolateral LV wall) in most of the patients (71.1%). In those patients without lateral or posterolateral branches, the LV lead was placed using other branches.

Analysis of LV Lead Pacing Threshold

Differences in LV parameters between men and women are listed in [Table 3](#). LV pacing threshold in women was significantly higher than that in men (men, 1.42 ± 0.98 V; women, 2.02 ± 1.20 V, $P=0.003$). No significant differences were observed in either LV lead impedance or amplitude between men and women. Comparison of LV pacing threshold categorized by gender and LV lead position is shown in [Figure 2](#). Men with an LV lead in any mid-lateral wall position (mid-an-

Table 3. Gender and LV Pacing Parameters

	Men	Women	P-value
LV pacing threshold (V)	1.42 ± 0.98	2.20 ± 1.20	0.003
LV impedance (Ω)	931 ± 350	1014 ± 352	0.98
LV amplitude (mV)	13.95 ± 7.38	12.06 ± 8.08	0.90

Data given as mean $\pm$ SD. LV, left ventricular.

terolateral, mid-lateral or mid-posterolateral wall) had significantly lower pacing thresholds than those with leads in non-mid-lateral walls (1.29 ± 0.86 V vs. 1.81 ± 1.18 V, $P=0.008$). Women with an LV lead in any mid-lateral wall had significantly higher pacing threshold than men with any mid-lateral LV lead (1.29 ± 0.86 V vs. 1.91 ± 1.18 V, $P=0.003$). Comparison of LV pacing threshold based on LV lead position defined

Table 4. Factors Contributing to High Pacing Threshold

Parameters	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Gender (Female)	2.75	1.17–6.20	0.021	3.57	1.41–8.97	0.008
Age (≥65 years)	2.44	1.16–5.36	0.018	1.92	0.85–4.50	0.116
BMI (≥30 kg/m ²)	1.11	0.46–2.54	0.807	–	–	–
Ischemic cardiomyopathy	2.28	1.07–5.10	0.036	2.07	0.91–4.96	0.082
Ejection fraction (≥30%)	2.18	1.05–4.61	0.037	1.86	0.85–4.14	0.133
Position of LV lead (non-optimal position)	3.00	1.40–6.35	0.004	2.70	1.20–6.00	0.016
QRS duration (≥150ms)	1.42	0.69–3.00	0.340	–	–	–

CI, confidence interval; OR, odds ratio.

along the long axis is shown in **Figure 3**. Average pacing thresholds of the basal, mid-ventricular and apical group were 2.16 ± 1.35 V, 1.44 ± 0.98 V and 1.50 ± 0.87 V, respectively. The basal group had significantly higher pacing threshold than the mid-ventricular and apical group ($P=0.001$ and 0.03 , respectively). Multivariate analysis identified gender and LV lead position as independent risk factors associated with high pacing threshold (**Table 4**). LV lead complication rate was compared between patients with normal (182 patients) and high pacing threshold (35 patients). During an average follow-up period of 3.3 years, no significant difference was observed in LV lead diaphragmatic pacing (9/182, 4.9% vs. 3/35, 8.6%) and LV lead dislodgement (10/182, 5.5% vs. 4/35, 11.4%) between patients with normal and high LV pacing threshold.

Discussion

The present data show that a higher percentage of women than men do not have optimal CS branches for LV lead placement. These data are consistent with that of Blendea et al, who performed a detailed analysis of CS anatomy in patients with CRT.²⁰ They found that 9% of patients did not have a lateral branch and that women had smaller diameter CS branches and shorter lateral branches compared to men.

In spite of the anatomical differences in CS anatomy between men and women, the proportion of patients with successful LV lead placement in the mid-lateral wall was similar between men and women in the present study. This suggests that in most cases an LV lead can be positioned at the LV mid-lateral area, as defined on biplane fluoroscopy, using available CS branches. Recent research shows that LV leads positioned in the apical region are associated with an unfavorable outcome, suggesting that this lead location should be avoided in CRT.^{25,28,29} Although not statistically significant, there was a trend for women to have the LV lead placed in any basal wall or anterior wall more often than men (men vs. women, 11.7% vs. 21.6%, $P=0.12$), suggesting that short and narrow lateral branches lead to the LV lead being placed in the basal and anterior area more often, as an alternative in women. Placing the LV lead at a basal or an anterior area may be useful for avoiding placement in the undesirable apical region.

It was also found that women have higher LV lead pacing threshold than men. One possible explanation for such a higher pacing threshold in women is the use of less favorable LV lead positions, resulting from anatomical disadvantages such as fewer alternative sites for LV lead placement, and narrower or shorter CS branches. In the present study, LV leads positioned in the basal LV wall had significantly higher pacing thresholds than LV leads positioned in the mid-ventricular and apical LV wall. But even in patients in whom the LV lead was

positioned in the mid-lateral LV wall, the average pacing threshold was higher in women than in men. On univariate analysis, ischemic cardiomyopathy was found to be an independent predictor for higher pacing threshold. Although this could be explained by regional tissue scarring caused by ischemic necrosis, detailed analysis of scar area associated with coronary artery disease was not performed in this study. Patients with high LV pacing threshold had a tendency to have more diaphragmatic pacing and/or LV lead dislodgement, but the difference was not statistically significant due to the small number of patients with these complications. Although high pacing threshold could potentially cause earlier depletion of a CRT battery, the present follow-up period (3.3 years) was not long enough to investigate the relationship between high pacing threshold and device longevity.

Study Limitations

This was a retrospective analysis of consecutive patients who underwent CRT and therefore is subject to the limitations inherent in any retrospective study.

Conclusions

A disadvantageous CS anatomy for CRT is more often observed in women compared to men. LV lead pacing threshold was higher in women due to this anatomical disadvantage. Implanting physicians should consider these gender differences during LV lead placement to ensure success and to maximize CRT benefits.

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