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Gender differences in electro-mechanical characteristics of left bundle branch block: Potential implications for selection and response of cardiac resynchronization therapy

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ABSTRACT

Background: Female patients are underrepresented in cardiac resynchronization therapy (CRT) trials, although they show better CRT response compared to males and at shorter QRS durations. We hypothesized that differences in left bundle branch block (LBBB) characteristics and mechanical dyssynchrony might explain this gender disparity.

Methods: Patients presenting with true LBBB-morphology (including mid-QRS notching) on surface electrocardiograms (ECG) were selected. LBBB QRS duration ($QRSD_{LBBB}$) was measured automatically on the ECG. Left ventricular dimensions were assessed by two-dimensional echocardiography. Mechanical dyssynchrony was assessed by the presence of septal flash (SF) on echocardiography.

Results: The study enrolled 1037 patients (428 females). Female LBBB patients had smaller $QRSD_{LBBB}$ compared to male LBBB patients (142 [22]ms versus 156 [24]ms, $p < 0.001$). In a multivariate analysis, sex and left ventricular end-diastolic diameter (LV_{EDD}) were independent predictors of $QRSD_{LBBB}$. $QRSD_{LBBB}$ can be corrected for sex and LV_{EDD} using a simplified formula: corrected-$QRSD_{LBBB} = QRSD_{LBBB} + 0.5 \times (50 - LV_{EDD}) - 10$ (if male). SF was more prevalent in females compared to males (60% versus 43%, $p < 0.001$). Women revealed significantly more SF in narrow $QRSD_{LBBB}$ groups compared to men: 65% versus 13% ($p < 0.001$) with $QRSD_{LBBB}$ 120–129 ms, 66% versus 18% ($p < 0.001$) with $QRSD_{LBBB}$ 130–139 ms and 63% versus 31% ($p < 0.001$) with $QRSD_{LBBB}$ 140–149 ms. At $QRSD_{LBBB} > 150$ ms, there were no differences in SF prevalence between females and males.

Conclusion: Female patients show true LBBB morphology at shorter QRSD and have more frequent mechanical dyssynchrony at shorter QRSD compared to males. This might explain the better CRT response rates at shorter QRSD in females.

1. Introduction

QRS duration (QRSD) and QRS morphology are the key variables to select patients eligible for cardiac resynchronization therapy (CRT) [1,2]. The largest benefit of CRT occurs in patients with left bundle branch block morphology (LBBB) and wide QRSD [3,4]. Therefore, guidelines favor CRT in patients with LBBB morphology and wide QRSD (>150 ms) and do not recommend CRT when QRSD is <130 ms, even in the presence of LBBB [1,2].

Gender disparity in CRT response has been reported previously [5–7]. Although women are underrepresented in clinical trials, female LBBB patients tend to show better CRT response even at shorter QRSD compared to male LBBB patients.

In this study, we hypothesized that differences in LBBB characterization and prevalence of mechanical dyssynchrony might explain gender disparity in CRT selection and CRT response. As such, we evaluated whether, 1) QRSD in patients with LBBB differs between sexes, 2) LBBB QRSD should be corrected for sex differences in body size or cardiac dimensions and 3) prevalence of mechanical dyssynchrony differs between sexes.

2. Methods

2.1. Selection of LBBB patients

Between January 2013 and September 2016, patients presenting with LBBB morphology on a standard twelve lead electrocardiogram (ECG) at the cardiac department of the University Hospital of Ghent were screened and enrolled in this retrospective study. Our study population consisted mainly of ambulatory patients who underwent an ECG at our department. Reasons for ECG-registration were diverse: ambulatory follow-up of cardiac patients, routine ECG screening and symptom-related ECGs (Table 1). ECGs were recorded with MAC 5500 ECG recording devices (GE Healthcare, Waukesha, WI, USA) and stored digitally in a MUSE Cardiology Information system (GE Healthcare). All ECGs

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were evaluated by one electrophysiologist, specialized in ECG reading and "true LBBB" diagnosis was defined according to the American Heart Association, American College of Cardiology Foundation and Heart Rhythm Society. This definition includes a QRSD ≥ 120 ms, QS or rS in lead V1 and broad notched or slurred R waves in two adjacent leads among leads I, aVL, V5 and V6 [8]. This definition of true LBBB included the presence of mid-QRS notching and slurring in the left lateral leads as this differentiates true LBBB from QRS prolongation due to left ventricular hypertrophy [9,10]. Patients who did not meet the criteria for true LBBB, although initially labeled as LBBB, were considered as LBBB-like intraventricular conduction delay. Patients were divided as having ischemic and non-ischemic heart disease based on a history of acute coronary syndrome or significant coronary artery disease requiring percutaneous or surgical revascularization".

The study was approved by the ethic committee of the University Hospital of Ghent.

2.2. Measurements of LBBB characteristics

QRSD ($QRSD_{LBBB}$) was measured automatically using the Marquette™ 12SL algorithm in the ECG recording devices. This algorithm measures $QRSD_{LBBB}$ as a global QRSD, which is calculated from the earliest beginning until the latest ending of the QRS complex in all leads as recommended by guidelines [8]. This automated algorithm was previously validated by comparing it to manual QRSD measurements using digital calipers [11].

Besides $QRSD_{LBBB}$, time to first QRS notching ($QRSD_{Notch}$), time to R-peak in the lateral leads ($QRSD_{Peak}$), presence of lateral q-wave (Q_{Lat}), max R-wave amplitude in lateral limb leads (QRS_{Ampl}), and QRS axis (QRS_{Axis}) were analyzed.

2.3. Echocardiographic assessment of LBBB patients

Echocardiographic examinations within 3 months of the ECG recording date were considered for further analysis. All echocardiographic examinations were performed by experienced echocardiographers using commercially available systems (GE Healthcare Ultrasound Vivid 7 and GE Healthcare Ultrasound Vivid E9, Vingmed, Horton, Norway; Philips Ultrasound iE 33, Best, Netherlands). Standard two-dimensional cine-loops were recorded for parasternal long and short axes and apical four chamber views. Left ventricular (LV) dimensions were measured in conventional parasternal views: LV enddiastolic diameter (LV_{EDD}), LV endsystolic diameter (LV_{ESD}), interventricular septal wall thickness (IVSD) and posterior wall thickness (PWD). Relative wall thickness (RWT) was calculated as $2 \times PWD/LV_{EDD}$ [12]. LV mass (LV_{MASS}) was calculated as $LV_{MASS}\,(g) = 0.8 \times (1.04 \times ([LV_{EDD} + IVSD + PWD]^3 - LV_{EDD}^3)) + 0.6$ [13]. LV_{EDD}, LV_{ESD} and LV_{MASS} were indexed for body surface area (BSA): LV_{EDDi}, LV_{ESDi} and LV_{MASSi}. The left ventricular ejection fraction (EF) was judged as normal (>55%), moderately reduced (36%–55%) and severely reduced (≤35%).

2.4. Assessment of mechanical dyssynchrony

Mechanical dyssynchrony was assessed by the presence of septal flash (SF) on echocardiography. SF refers to a specific echocardiographic pattern in which a rapid, pre-ejection, leftward motion (right to left) of the septum occurs, followed by late contraction of the lateral left ventricular wall, causing a left to right motion of the septum. This SF pattern is an easy and objective parameter to diagnose LV intraventricular dyssynchrony and the presence of SF among LBBB patients is highly predictive of CRT response [14–17].

Two echocardiography experts, blinded to the ECGs, reviewed all echocardiographic studies offline using EchoPAC version 7.1.13 for the GE scanning systems and Xcelera viewer R3 version 3.3.1 2013 for Philips scanning system. The presence of SF was assessed visually (parasternal short axis, parasternal long axis or apical views) as validated in prior studies [17,18]. This visual assessment of SF has been shown as a reliable and accurate method to assess mechanical dyssynchrony of the LV [18]. Previously, we validated this 'visual eyeballing' detection of SF at our center with SF assessments by 2-dimensional

Table 1
Patient characteristics overall, and gender specified.

	All patients	Female patients	Male patients	*p*-Value
	$n = 1037$	$n = 428$	$n = 609$	
Reasons for ECG registration n (%)				
Symptom-related ECG				
Chest pain	129 (12)	38 (8.9)	91 (15)	$\mathbf{p = 0.004}$
Dyspnoea	69 (6.7)	26 (6.1)	43 (7.1)	$p = 0.531$
Syncope	30 (2.9)	16 (3.7)	14 (2.3)	$p = 0.173$
Palpitations	39 (3.8)	16 (3.7)	23 (3.7)	$p = 0.974$
Routine ECG				
Screening	123 (12)	49 (11)	74 (12)	$p = 0.731$
Cardiac follow-up	647 (62)	283 (66)	364 (60)	$\mathbf{p = 0.038}$
Baseline characteristics				
Age (yrs)	70 ± 16	71 ± 16	69 ± 16	$\mathbf{p = 0.002}$
Length (cm)	168 ± 11	160 ± 7	172 ± 9	$\mathbf{p < 0.001}$
Weight (kg)	77 ± 19	69 ± 16	80 ± 16	$\mathbf{p < 0.002}$
Body mass index (kg/m^2)	27 ± 5.5	27 ± 5.7	27 ± 4.9	$p = 0.735$
Body surface area (BSA) (m^2)	1.86 ± 0.23	1.72 ± 0.19	1.93 ± 0.21	$\mathbf{p < 0.001}$
Clinical status				
Blood pressure systolic (mm Hg)	120 ± 39	123 ± 39	118 ± 38	$p = 0.055$
Blood pressure diastolic (mm Hg)	62 ± 21	64 ± 22	62 ± 20	$p = 0.515$
Heart rate (beats/min)	75 ± 21	76 ± 19	74 ± 21	$p = 0.027$
NYHA ≥ II	289 (28)	108 (25)	181 (30)	$p = 0.499$
Atrial fibrillation	79 (7.6)	37 (8.6)	42 (6.9)	$p = 0.136$
Cardiovascular risk factors n (%)				
Smoking	78 (7.5)	26 (6.1)	52 (8.5)	$\mathbf{p < 0.001}$
Hypercholesterolemia	98 (9.5)	45 (10.5)	53 (8.7)	$p = 0.373$
Arterial hypertension	464 (44.6)	197 (46.0)	265 (43.5)	$p = 0.228$
Diabetes	215 (20.7)	78 (18.2)	137 (22.5)	$p = 0.149$
Underlying heart disease n (%)				
Ischemic heart disease	376 (36.3)	105 (24.5)	271 (44.5)	$\mathbf{p < 0.001}$
Congenital heart disease	35 (3.4)	14 (3.3)	21 (3.4)	$p = 0.908$
Valvular heart disease	182 (17.6)	74 (17.3)	108 (17.7)	$p = 0.617$
Medical treatment				
Betablockers	401 (38.7)	125 (29.2)	276 (45.3)	$\mathbf{p < 0.001}$
ACE-inhibitors	294 (28.3)	110 (25.7)	184 (30.0)	$p = 0.170$
Diuretics	156 (15.0)	48 (11.2)	108 (17.7)	$\mathbf{p = 0.011}$
Class 1C antiarrhythmics	15 (1.4)	11 (2.6)	4 (0.7)	$\mathbf{p = 0.019}$
Class 3 antiarrhythmics	80 (7.7)	21 (4.9)	59 (9.7)	$\mathbf{p = 0.005}$
Echocardiographic measurements				
Enddiastolic diameter (mm)	51 ± 10	47 ± 8	54 ± 10	$\mathbf{p < 0.001}$
Enddiastolic diameter/BSA (mm/m^2)	28 ± 6	28 ± 5	28 ± 6	$p = 0.321$
Endsystolic diameter (mm)	34 ± 13	30 ± 10	37 ± 13	$\mathbf{p < 0.001}$
Endsystolic diameter/BSA (mm/m^2)	17 ± 9	18 ± 7	19 ± 7	$\mathbf{p = 0.015}$
Left ventricular mass (g)	212 ± 78	171 ± 62	230 ± 85	$\mathbf{p < 0.001}$
Left ventricular mass/BSA (g/m^2)	116 ± 40	99 ± 33	119 ± 43	$\mathbf{p < 0.001}$
Relative wall thickness	0.42 ± 0.11	0.44 ± 0.12	0.40 ± 0.11	$\mathbf{p < 0.001}$

Bold values indicates significance at $p < 0.05$.