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Impact of QRS morphology on heart rate turbulence and heart rate variability after cardiac resynchronization therapy in patients with heart failure

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Abstract. – OBJECTIVE: Impairment of heart rate turbulence (HRT) and heart rate variability (HRV) are associated with poor prognosis in chronic heart failure (CHF). Although previous studies have demonstrated that patients with a left bundle branch block (LBBB) have a better outcome with cardiac resynchronization therapy (CRT), the effect of QRS morphology on HRV and HRT is not known. We aimed to evaluate the effect of QRS morphology on HRV and HRT after CRT implantation in patients with CHF.

PATIENTS AND METHODS: Patients who had been implanted a CRT device with cardioversion-defibrillation feature were included to the study. Forty-three patients with LBBB (group 1) were compared with 21 patients without LBBB (group 2). HRV and HRT parameters were compared before and one month after CRT implantation.

RESULTS: We compared the echocardiographic and electrocardiographic changes in both groups after CRT. Cardiac output (CO) was found to be significantly much more increased in group 1 (1.1 ± 0.4 *vs.* 0.6 ± 0.4, p = 0.001). Similarly, except SDNN and LF, all HRT and HRV parameters were significantly changed in the patients with LBBB (TO 1.4 ± 0.3 *vs.* 1.2 ± 0.2, p = 0.001; TS -1.8 ± 0.7 *vs.* -0.9 ± 0.7, p = 0.001; RMSSD -15.7 ± 9.9 *vs.* -6.3 ± 6.2, p = 0.001; PNN50 -7.0 ± 4.6 *vs.* -1.7 ± 1.1, p = 0.001; HF -13.3 ± 6.7 *vs.* -4.3 ± 3.5, p = 0.001; LF/HF 1.9 ± 0.4 *vs.* 1.5 ± 0.2, p = 0.001) compared to those without LBBB. Lineer regression analysis showed that the CO (β = 0.2, t = 2.8, p = 0.007) and QRS configuration (β = 0.6, t = 0.5, p = 0.001) were independent parameters affecting TO.

CONCLUSIONS: HRV and HRT are improved after CRT but these improvements are more remarkable in patients with LBBB. CO, QRS configuration (but not duration) were two independent parameters affecting TO, LF and LF/HF ratio after CRT.

Key Words:
Heart failure, Heart rate variability, Heart rate turbulence, Cardiac resynchronization therapy, QRS morphology.

Introduction

Chronic heart failure (CHF) is characterized by permanent neurohumoral activation, i.e. increased sympathetic activity, depressed parasympathetic activity and activation of renin-angiotensin-aldosteron system which are critical mechanisms responsible for increased mortality[1,2]. Heart rate turbulence (HRT) and heart rate variability (HRV) are not only a measure of cardiac autonomic functions and baro-receptor activity, but also a predictor of mortality in patients with CHF[3,4].

Cardiac resynchronization therapy (CRT) is accepted as a treatment strategy for a subgroup of patients with heart failure and an uncoordinated contraction pattern of the ventricles[5]. It has been shown that CRT improves hemodynamic function[6], heart failure symptoms, exercise capacity and reduces morbidity and mortality rates[7]. CRT also induces acute effects in autonomic functioning[8] and baroreceptor sensivity[9]. Improvement in autonomic functions after CRT were demonstrated by HRV and HRT analysis in patients with CHF[10-12]. Despite the encouraging results, the beneficial effect of CRT may vary significantly. A significant proportion of treated patients fail to benefit from this therapy[13]. Previous studies have demonstrated that patients with a left bundle branch block (LBBB) configuration have a high likelihood of responding favourably

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to CRT[14]. However, the effect of QRS morphology on HRV and HRT is not known. In this study, we evaluated the effect of QRS morphology on HRV and HRT after CRT implantation in patients with CHF.

Patients and Methods

This is an observational, cross-sectional study. Patients admitted to outpatient clinics between May 2013 and February 2015 who had systolic heart failure with a left ventricular ejection fraction (LVEF) ≤ 35% and had been implanted a CRT device with cardioversion-defibrillation feature according to the relevant guidelines were included[15].

Patients with atrial fibrillation were excluded due to inability of HRV and HRT measurement in these group. Also to eliminate the direct effects of pacemaker functioning on HRV and HRT parameters, CRT patients with an atrial sense < 90% were excluded. Other exclusion criteria were: congenital heart disease, chronic systemic disease, significant valvular heart disease, hypertrophic cardiomyopathy and cor-pulmonale. At the time of enrollment, all the patients were on standard heart failure medication. Medication kept constant during the study. Complete transthoracic echocardiography was performed to all patients. Left ventricle ejection fraction (LVEF), left ventricular dimensions, left ventricle end-systolic volume, left ventricle outflow tract time-velocity integral area (LVOT-TVI) and stroke volume (SV) were evaluated according to the recommendations of American Society of Echocardiography[16]. Cardiac output index (COi) was calculated from the continuous wave aortic outflow spectra: Left ventricle outflow tract diameter was measured from a 2D parasternal long-axis view. After the pacemaker implantation and optimization, measurements were repeated.

Biventricular pacemaker leads were inserted via left subclavian vein. The leads were inserted to the right atrial appendage, right ventricular apex and coronary sinus (90% in posterolateral vein). Doppler echocardiographic measurements were used for the optimization of atrio-biventricular delay after pacemaker implantation[17].

The study protocol was approved by the institutional Ethical Committee and written informed consent was obtained from all patients.

Baseline characteristics, medications history, vital signs, and functional status of the patients were evaluated at the time of inclusion. HRT and HRV parameters were collected and they were compared before and one month after CRT implantation.

A 24-hour electrocardiogram (ECG) Holter recording was performed to evaluate HRT and HRV parameters in both groups.

Heart Rate Variability and Heart Rate Turbulence Measurements

A three-channel digitized Holter ECG recorder was used for HRV and HRT measurements. An experienced physician who was totally blinded to the study population evaluated 24-hour Holter ECG recordings. The data were manually preprocessed before evaluating. Recordings with sufficient quality for analysis and lasting for at least 18 hours were included. If these criteria were not met, the recordings were repeated.

Time-domain HRV indices, root mean square of the successive differences (RMSSD), the standard deviation of all normal-to-normal (NN) intervals (SDNN), and the proportion of adjacent R-R intervals differing by > 50 milliseconds in the 24-hour recording (pNN50) were measured. Mean R-R interval was also calculated. The measurements were done according to the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology[4]. The high frequency (HF) component (0.15-0.40 Hz), the low frequency (LF) component (0.04-0.15 Hz) and the total power were measured for frequency-domain analysis of HRV. To give the relative changes in the frequency-domain the normalized HF power (HFnu = 100 × HF power/total power), normalized LF power (LFnu = 100 × LF power/total power) and low/high frequency power ratio (LF/HF ratio = LF power/HF power) were measured. Spectral analysis was performed with short-segments with averaging of parameters.

Computation of HRT

All analysis were performed by a blinded physician to clinical information. In brief, turbulence onset (TO) is the difference between the post-premature ventricular contraction (PVC) pause (R_{+1}, R_{+2}), and the two beats preceding PVC (R_{-1}, R_{-2}) as a percentage of preceding CLs:

$$TO = 100 \times \frac{(R_{+1} + R_{+2}) - (R_{-1} + R_{-2})}{R_{-1} + R_{-2}}$$

where TO < 0% is normal.

Turbulence slope (TS) is the steepest slope of linear regression lines for sequences of five consecutive post-PVC intervals up to 20 beats.

After manual review of the 24-hour Holter tracings, TO and TS were determined according to the previously published method (18).

Statistical Analysis

All statistical analysis were performed by the SPSS statistical software (SPSS for windows 15, SPSS Inc., Chicago, IL, USA). Continuous variables were given as mean ± SD; categorical variables were defined as numbers (percentages). Kolmogorov-Smirnov test was used for the determination of normal distribution. Independent samples *t*-test and Mann-Whitney U test were used for continuous variables and the χ^2 test was used for the categorical variables. Linear regression analysis was used to detect effects of study variables on HRV and HRT parameters. Analysis of covariance (ANCOVA) was then performed to verify the influence of CRT on results obtained in the parametric tests (independent *t*-test). A *p* value of < 0.05 was defined for statistical significance. All tests of significance were two-tailed.

Results

Fourty-three patients with LBBB who were implanted CRT-ICD were compared with 21 patients without LBBB (4 with right bundle branch block, 17 with non-specific interventricular conduction delay).

There were no differences in both groups regarding baseline characteristics, clinical variables, HRT and HRV parameters (Table I). Besides cardiac output (CO), all HRT and HRV parameters were significantly changed 1 month after CRT implantation in both groups (Table II).

When we compared the echocardiographic and electrocardiographic changes in both groups after CRT, CO was found to be significantly much more increased in group 1 (1.1 ± 0.4 *vs*. 0.6 ± 0.4, $p = 0.001$). Similarly, except SDNN (4.8 ± 4.5 msec *vs*. 3.3 ± 5.1 msec, $p = 0.2$) and LF (8.5 ± 5.4 *vs*. 6.3 ± 3.5, $p = 0.06$), all HRT and HRV parameters were significantly changed in the patients with LBBB (TO 1.4 ± 0.3 *vs*. 1.2 ± 0.2, $p = 0.001$; TS -1.8 ± 0.7 *vs*. -0.9 ± 0.7, $p = 0.001$; RMSSD -15.7 ± 9.9 *vs*. -6.3 ± 6.2, $p = 0.001$; PNN50 -7.0 ± 4.6 *vs*. -1.7 ± 1.1, $p = 0.001$; HF -13.3 ± 6.7 *vs*. -4.3 ± 3.5, $p = 0.001$; LF/HF 1.9 ± 0.4 *vs*. 1.5 ± 0.2, $p = 0.001$) compared to those without LBBB.

The changes in HRV and HRT parameters after CRT were found to be correlated with the changes in the cardiac output (TO, r = -0.5, $p = 0.001$; TS, r = 0.8, $p = 0.001$; SDNN, r = 0.8, $p = 0.001$; PNN50, r = 0.6, $p = 0.001$; LF, r = 0.3, $p = 0.02$; HF, r = 0.6, $p = 0.001$; LF/HF, r = -0.4, $p = 0.004$).

Linear regression analysis showed that the only independent parameter affecting RMSSD ($\beta = 1.3$, $t = 6.1$, $p = 0.001$), PNN50 ($\beta = 1.2$, $t = 0.6$, $p = 0.001$), HF ($\beta = 1.5$, $t = 7.3$, $p = 0.001$) was CO after CRT. In addition to the CO ($\beta = 0.2$, $t = 2.8$, $p = 0.007$), also QRS configuration ($\beta = 0.6$, $t = 0.5$, $p = 0.001$) was an independent parameter affecting TO. Similarly, CO and QRS configuration were two independent parameters affecting LF ($\beta = 0.8$, $t = 3.1$, $p = 0.003$ and $\beta = 0.6$, $t = 4.1$, $p = 0.001$, respectively) and LF/HF ratio ($\beta = -0.8$, $t = -3.4$, $p = 0.001$ and $\beta = 0.4$, $t = 2.9$, $p = 0.006$, respectively) after CRT.

Discussion

Main results of our study are: (1) Both HRV and HRT parameters were improved after CRT; (2) Improvements in cardiac output, HRT and most HRV parameters were more remarkable in patients with LBBB; (3) The changes in HRV and HRT parameters after CRT were well correlated with cardiac output; (4) In addition to the CO, QRS configuration (but not duration) was the other independent parameter affecting TO, LF and LF/HF ratio after CRT.

Previous studies have shown that HRV and HRT are improved after CRT in patients with CHF[10-12,19]. The improvement in the HRV and HRT parameters were also associated with clinically good responders to CRT in these studies. We enrolled CHF patients with CRT-ICD and compared the HRT and HRV parameters in different QRS configurations.

Despite the encouraging results from CRT, the beneficial effect of CRT may vary significantly. Up to approximately 45% of treated patients fail to benefit from this therapy or the heart failure symptoms deteriorated which were selected according to the QRS duration[13]. Recently, many studies have attempted to identify potential factors for predicting CRT response before pacemaker implantation, and reported that factors such as sex[13], HF etiology[13], QRS duration[13], history of tachycardia[13], persistent atrial fibrillation[20] were associated with CRT response. Lin et

Table I. Comparison of baseline characteristics of both groups.

Variables	Group 1 (n = 43)	Group 2 (n = 21)	p
Age (years)	64.4 ± 8.9	65.2 ± 8.8	NS
Male, n (%)	30 (70%)	14 (67%)	NS
Ischaemic etiology, n (%)	32 (74%)	15 (71%)	NS
Hypertension, n (%)	29 (67%)	15 (71%)	NS
Diabetes mellitus, n (%)	12 (28%)	7 (33%)	NS
Smoking, n (%)	15 (37%)	8 (38%)	NS
NYHA			
Class II, n (%)	27 (66%)	16 (34%)	NS
Class III, n (%)	13 (62%)	8 (38%)	
Medications			
ACE-I/ARBs, n (%)	35 (81%)	18 (86%)	NS
Beta blockers, n (%)	30 (70%)	14 (67%)	NS
Statins, n (%)	12 (28%)	7 (33%)	NS
Digoxin, n (%)	12 (28%)	7 (33%)	NS
Spironolactone, n (%)	31 (72%)	17 (80%)	NS
Furosemide, n (%)	40 (93%)	19 (90%)	NS
Left ventricular ejection fraction (%)	26.3 ± 5.4	24.6 ± 6.3	NS
Cardiac output (l/min)	2.8 ± 0.7	2.7 ± 0.6	NS
QRS durations (msec)	148.6 ± 6.8	151.1 ± 6.6	NS
Mean heart rate (rate/min)	87.5 ± 12.8	88.8 ± 14.2	NS
Heart rate turbulence parameters			
Turbulence onset	0.9 ± 0.4	1.2 ± 1.1	NS
Turbulence slope (msec/RR)	1.5 ± 1.3		NS
Heart rate variability parameters			
SDNN (msec)	100.2 ± 34.4	92.9 ± 32.4	NS
RMSSD (msec)	31.6 ± 9.2	36.4 ± 10.1	NS
PNN50 (%)	7.7 ± 2.8	7.4 ± 2.7	NS
LFnu	38.6 ± 12.7	41.8 ± 9.9	NS
HFnu	22.9 ± 7.8	22.3 ± 6.9	NS
LF/HF	3.8 ± 0.6	3.9 ± 0.4	NS

Data are expressed as mean ± SD and number of patients and percentages. **t*-test for independent samples and Chi-square test for categorical variables. ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; HF: high frequency power; HFnu: normalized high frequency power; LFnu: normalized low frequency power; LF: low frequency power; NS-not significant; NYHA: New York Heart Association; pNN50: proportion of adjacent R-R intervals differing by > 50 milliseconds in the 24-hour recording; RMSDD: square root of the mean squared differences of successive normal-to-normal intervals; SDNN: standard deviation of all normal-to-normal intervals; SDANN, standard deviation of the average normal-to-normal intervals calculated over 5-minute periods of the entire recording.

Table II. Changes in parameters after cardiac resynchronization therapy in both groups.

Variables	Group 1		Group 2	
	Baseline	1st month	Baseline	1st month
Cardiac output (l/min)	2.8 ± 0.7	3.8 ± 0.7*	2.7 ± 0.6	3.2 ± 0.7*
Turbulence onset	0.9 ± 0.4	-0.6 ± 0.3*	1.0 ± 0.4	-0.8 ± 0.3*
Turbulence slope	1.5 ± 1.3	3.4 ± 1.5*	1.2 ± 1.1	2.1 ± 1.3*
SDNN	100.2 ± 34.4	95.4 ± 33.2*	92.9 ± 32.4	88.7 ± 31.5*
RMSSD	31.6 ± 9.2	50.3 ± 11.1*	36.4 ± 10.1	42.8 ± 9.4*
PNN50	7.7 ± 2.8	14.8 ± 5.2*	7.4 ± 2.7	9.0 ± 2.8*
LFnu	38.6 ± 12.7	31.1 ± 8.9*	41.8 ± 9.9	36.5 ± 8.2*
HFnu	22.9 ± 7.8	36.3 ± 10.8*	22.3 ± 6.9	26.6 ± 9.3*
LF/HF	3.8 ± 0.6	1.9 ± 0.3*	3.9 ± 0.4	2.5 ± 0.4*

*$p < 0.05$ when compared with baseline values.

al[21] found that QRS morphology is the only independent predictor for CRT response, and Kaplan-Meier survival analysis revealed that patients with non-LBBB had significantly higher rates of mortality or heart failure rehospitalization as compared with those with LBBB. This result is consistent with 2 recently published reports[22,23] that showed patients with LBBB derived favorable outcomes from CRT-D; nevertheless, no evidence was found in terms of clinical and echocardiographic benefits from CRT-D in patients with no LBBB.

Beneficial effects of CRT on cardiac autonomic functions may be explained by these factors: (1) Left ventricular dyssynchrony causes cardiac sympathetic activation and optimization of mechanical activation pattern by CRT is one reason for decreasing cardiac sympathetic activity[24,25]; (2) CRT acutely decreases left ventricular end-diastolic pressure and thereby positively affects vagal afferent mecaho-receptor functions[26]; (3) CRT acutely increases the maximal rate of left ventricular pressure change (dP/dt max)[27]; (4) Changes in systolic blood pressure may explain baroreceptor sensitivity improvement due to biventricular pacing[28]. Similarly, we found that the increase in cardiac output and basal QRS configuration are two predictors of improvement in HRT and HRV parameters.

Conclusions

As a result, we found that HRV and HRT parameters are improved after CRT, but these improvements are more remarkable in patients with LBBB. Cardiac output, QRS configuration (but not duration) were two independent parameters affecting TO, LF and LF/HF ratio after CRT.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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