Cardiac Resynchronization Therapy Improves Exercise Heart Rate Recovery in Patients With Heart Failure

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ABSTRACT

Background: Heart rate (HR) recovery (HRR), defined as the rate of decline in HR immediately following cessation of exercise, is influenced by autonomic function. Cardiac resynchronization therapy (CRT) improves cardiac autonomic functions in HF. We aimed to evaluate the effects of CRT on cardiac autonomic function assessed by HRR.

Methods: Forty-eight patients (62.3±10.7 years; 37 men; LV ejection fraction 24.8 ± 4.1%) with HF were enrolled. A treadmill exercise testing was conducted in all patients by using Modified Naughton protocol before and 6 months after CRT. HRR indices were calculated by subtracting first, second and third minute HR from the maximal HR and designated as HRR1, HRR2 and HRR3. Left ventricular reverse remodeling (LVRM) was quantified as the percentage of decline in LV end systolic volume after CRT.

Results: Mean HRR1 (13.0±5.9 vs 17.9 ± 8.9, p=0.001), HRR2 (20.5 ± 9.3 vs 23.8 ± 11.3, p=0.001) and HRR3 (25.7 ± 11.1 vs 29.2 ± 12.0, p=0.001) values improved after CRT. Pearson’s analyses revealed a good positive correlation between LVRM and ΔHRR1 (r=0.642, p=0.001) and a moderate correlation between reduction LVRM and ΔHRR2 (r=0.591, p=0.033) and ΔHRR3 (r=0.436, p=0.001).

Conclusions: CRT favorably alters the cardiac autonomic functions. HRR indices improved after CRT and degree of improvement in HRR indices correlated with LVRM.

Keywords: Cardiac resynchronization therapy, exercise, heart failure, heart rate recovery
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Kalp Yetmezliği Olan Hastalarda Kardiyak Resenkrzonizasyon Tedavisinin Kalp Hızı Toparlanması Üzerine Etkisi

ÖZET

Amaç: Kalp hızı (KH) toparlanma zamanı egzersizden hemen sonra kalp hızındaki düşme olarak tanımlanır ve otonomik işlevlerden etkilenir. Kardiyak resenkrzonizasyon tedavisi (KRT) kalp yetmezliğinde otomomik işlevleri iyileştirir. KRT’nin kardiyak otonomik işlevleri iyileştirir. KRT’nin kardiyak otonomik işlevleri üzerindeki etkilerini değerlendirmeyi amaçladık.

Yöntemler: Kalp yetmezlikli 48 hasta (62.3 ± 10.7 yıl; 37 erkek sol ventrikül ejeksiyon %24. 8 ± 4 yıl) alındı. KRT öncesi ve altı ay sonrasında Modifiye Naughton protokolüyle egzersiz testi yapıldı. KHTZ indeksleri maksimum KH’den egzersiz sonrası birinci, ikinci ve üçüncü dakikadaki KH’ler çıkarılarak KHTZ1 KHTZ2 ve KHTZ3 bulundu. Sol ventrikül tersine yeniden şekillenmesi, KRT sonrası sol ventrikül sistal hacmindeki yüzdelik azalma ile derecelendirildi.

Bulgular: Ortalama KHTZ (13.0 ± 5.9’a karşın 17.9 ± 8.9 p= 0.001), KHTZ2 (20,05 ± 9.3’e karşın 23.8 ± 11.3 p= 0.001) ve KHTZ3’de (25.7 ± 11.1’e karşın 29.2 ± 12.0, p= 0.001) KRT sonrası artış görülüldü. Sol ventrikül tersine yeniden şekillenmesi ile ∆ KHTZ1 (r=0.642, p=0.001) arasında güçlü bir pozitif korelasyon; ∆ KHTZ2 (r=0.591, p=0.033) ∆ KHTZ3 (r=0.4361, p=0.001) arasında orta derecede bir pozitif korelasyon saptandı.

Sonuç: KRT kardiyak otonomik işlevleri iyi yönde etkilemektedir. KHTZ indeksleri KRT’den sonra artış göstermektedir ve düzelenin boyutu sol ventrikül tersine yeniden şekillenmesiyle korelerdir.

ANAHTAR KELİMELER
Kardiyak resenkrzonizasyon tedavisi, kalp hızı toparlanması, kalp yetmezliği

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Introduction

Heart rate (HR) profiles during exercise testing are easy to perform and useful predictors of cardiovascular mortality. HR recovery (HRR) indices show the rate of decline in the HR after the cessation of exercise test and is defined as HR difference between the maximal HR on exercise and the HR during recovery phase (1-2). The rise in HR during exercise period is a consequence of an increase in sympathetic activity and a decrease in parasympathetic activity and the decline in HR during recovery is principally due to a reactivation of parasympathetic nervous system, mostly in the early recovery period (1-3).

Neuroendocrine dysregulation plays a central role in the pathogenesis of heart failure (HF) and is an important predictor of clinical outcomes. Adaptations of the autonomic nervous system, including excess sympathetic activity
and concomitant parasympathetic withdrawal, are among the manifestations of this maladaptive neuroendocrine imbalance (1-3). Several studies have shown that an impaired recovery of HRR during the first minute after graded exercise has been considered to reflect a diminished vagal activity and independently predicts an increased mortality (1-7). Moreover, the degree of the fall in HR in the first minute of recovery was found to be associated with cardiovascular mortality (4). Abnormalities in autonomic tone can be evaluated by this simple technique.

Cardiac resynchronization therapy (CRT) improves functional capacity, left ventricular (LV) systolic and diastolic functions, and survival in patients with refractory HF and left bundle branch block (8-12). It is also known that CRT can exert favorable effect on the mechanism that sustains the harmful autonomic dysfunction state and improvement in ventricular performance via resynchronization therapy shifts the cardiac autonomic balance toward a more favorable profile of less sympathetic and more parasympathetic activation (13-14). However, the effects of CRT on HRR are not studied yet.

Aims of this study were two folds; (I) to evaluate the effects of CRT on cardiac autonomic function assessed by HRR, (II) investigate whether an association existed between amelioration of LV reverse remodeling (LVRM) and improvement of HRR after CRT.

Patients and Methods

Study population

A total of 52 patients with symptoms of NYHA class III-IV HF, a LV ejection fraction (LVEF) $\leq 35\%$, sinus rhythm, and a QRS duration $\geq 120$ ms, despite optimal medical therapy, who were admitted to our department between March 2008 and December 2009, were enrolled in the study.

Patients were excluded if they were admitted with acute coronary syndrome in the last 3 months, had a life expectancy of $< 6$ months, sick sinus syndrome, heart transplantation, or electric storm. Of the patients, one could not undergo CRT implantation due to inappropriate coronary sinus anatomy. In addition, two patients were excluded from the study because of sick sinus syndrome and one patient was excluded because of poor echogenicity. The remaining 48 patients (37 males and 11 females; mean age $\pm$ SD, 62.3$\pm$10.7 years) were evaluated in this study.

All patients were evaluated in terms of age, gender, coronary artery disease (CAD) history, diabetes mellitus (DM), hyperlipidemia, hypertension (HT), and other concomitant diseases. All patients underwent a complete physical examination, and their height and weight were recorded. Transthoracic echocardiography, treadmill exercise test, and a Minnesota Living With Heart Failure Questionnaire (MLWHFQ), were performed in all patients one day before and six months after the CRT. MLWHFQ contains 21 questions refer to the signs and symptoms of HF, social relationships, physical and sexual activity, work and emotions. The answer for each question was chosen from a scale of 0 (none) to 5 (very much); the greater the score, the worse the quality of life (15).

Transthoracic echocardiography

The patients underwent transthoracic echocardiography at baseline and 6 months after CRT implantation. Echocardiographic examination was performed in the left lateral position using Vingmed System Five GE Ultrasound (General Electric, Horten, Norway) with a 2.5-3.5 MHz transducer from parasternal long- and short-axes, and apical two- and four-chamber vi-
ews. The measurements were based on the criteria proposed by the American Society of Echocardiography. From the parasternal long axis, the left ventricle end-diastolic diameter (LVEDD) and the left ventricle end-systolic diameter (LVESD) were measured using M-mode (at the mitral chordal level perpendicular to the long axis of the ventricle), and then LVEF was calculated. The endocardial boundaries were identified using end-diastolic and end-systolic images from the apical four-chamber view, and the LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) and LVEF were calculated with the modified Simpson’s method (16).

**Treadmill exercise testing**

A treadmill exercise testing was conducted in all patients by using Modified Naughton protocol. This is an incremental exercise test on a treadmill with 2-min stages and increments in both gradient and velocity simulating increments of about one metabolic equivalent (approximately 3.5 ml O2 x kg⁻¹ x min⁻¹). After achieving peak workload, all patients spent at least 3 minutes recovery without cool-down period. Patients performed same treadmill exercise test under VDD mode of biventricular pacing after six months of CRT. Exercise capacity was measured in metabolic equivalent levels (METs) at peak exercise. HRR indices were calculated by subtracting first, second and third minute heart rates from the maximal HR obtained during stress testing and designated as HRR1, HRR2 and HRR3.

**Device Implantation**

The LV pacing lead was inserted transvenously via the subclavian route. A coronary sinus venogram was routinely obtained before the introduction of LV lead. The LV electrode was placed in the posterolateral branch of the coronary sinus in 44 patients (91.6%), while it was placed in the antero-lateral branch of the coronary sinus in 4 patients (8.4%). The right ventricular lead was positioned at the apex and the right atrial lead in the atrial appendage.

Devices were programmed to increase biventricular pacing throughout the range of expected patient activity. Further optimization of atrioventricular (AV) delay was performed using Doppler echocardiography of transmural flow to provide the maximum LV filling time without compromising CRT (iterative method) and VV optimization was not performed (17-18). The AV delay was set at a value which provided maximum separation of the E and A waves, representing passive ventricular filling and atrial contraction, respectively.

**Definition of the Response**

LVRM was quantified as the percentage of decline in LVESV after CRT (19). A decrease of ≥15% in LVESV at the 6th month follow-up was defined as a positive echocardiographic response (19-20).

**Statistical Analysis**

Distribution of data was assessed by using a one-sample Kolmogorov–Smirnov test. Data are demonstrated as mean ± SD for normally distributed continuous variables, median (minimum–maximum) for skew-distributed continuous variables, and frequencies for categorical variables. For numerical variables, an independent sample t-test and the Mann–Whitney U-test were used for inter-group comparisons (responders vs non-responders). A comparison of the clinical, echocardiographic variables and HRR indices before and after CRT was performed by paired sample t-test or Wilcoxon signed-rank test. Inter- and intra-observer agreements for LV volumes and LVEF were assessed with intra- and inter-class
correlation coefficients and with the average difference between readings, corrected for their mean (variability). Percentage of change (\( \Delta \)) in HRR indices were compared by independent sample t-test. Pearson’s correlation analysis was used in order to assess the relationship between the LVRM and \( \Delta \)HRR indices. Statistical analysis of the data was conducted using SPSS 15 (SPSS Inc., Chicago, IL, USA) and two-tailed P-value <0.05 was considered statistically significant.

**Results**

Baseline clinical characteristics: Of the 48 patients (mean age, 62.3±10.7 years), 37 (77.1%) were males (mean age, 61.5±10.7 years) and 11 (22.9%) were females (mean age, 65.0±10.4 years). The etiology of HF was primarily ischemic (34 patients, 70.8%). DM was present in 18 (%37.5) patients. There was no complication of CRT device implantation and no patient required LV lead repositioning during follow-up. The programmed atrioventricular delay was 121.1±22.2ms. Baseline clinical, demographic and echocardiographic features of the patients are presented in Table 1.

All patients were re-evaluated at 6 months after CRT; 30 (62.5%) were responders (i.e., decline in LVESV ≥ 15%). The responder and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.3 ± 10.7</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>37 (77.1)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>35 (72.9)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>34 (70.8)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>147.50 ± 24.30</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
<td>4.45 ± 0.49</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>6.83 ± 0.79</td>
</tr>
<tr>
<td>LV end-systolic diameter, cm</td>
<td>5.64 ± 0.73</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>168.19 ± 48.83</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>116.00 ± 41.66</td>
</tr>
<tr>
<td>LV ejection fraction, %†</td>
<td>24.85 ± 4.12</td>
</tr>
<tr>
<td>LV fractional shortening, %‡</td>
<td>12.27 ± 3.21</td>
</tr>
<tr>
<td>ACE-I or ARB use, n (%)</td>
<td>48 (100)</td>
</tr>
<tr>
<td>( \beta )-Blocker use, n (%)</td>
<td>42 (87.5)</td>
</tr>
<tr>
<td>Diuretic use, n (%)</td>
<td>48 (100)</td>
</tr>
<tr>
<td>Digoxin use, n (%)</td>
<td>25 (52.0)</td>
</tr>
<tr>
<td>Spironolactone use, n (%)</td>
<td>24 (50.0)</td>
</tr>
</tbody>
</table>

† Measured by modified Simpson’s method; ‡ measured by M-mode echocardiography.

ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin– receptor blockers; CRT=cardiac resynchronization therapy; LV=left ventricular. Numerical variables were presented as the mean ± standard deviation and categorical variables were presented as percentages.
non-responder groups were similar with respect to age (64.1 ± 11.2 vs. 61.2 ± 10.4 years), gender distribution ([male/female] 21/9 vs. 16/2), hypertension (73.3% vs. 72.2%), DM (36.6% vs. 38.8%) and programmed atrioventricular delay (121.3±22.1 vs 119.0±24.1). In non-responder group, frequency of coronary artery disease (83.3% vs. 63.3%, p=0.04) was significantly higher than the responder group. Baseline HRR indices were similar between the responders and non-responders and none of the baseline HRR indices could predict response to CRT.

Reproducibility
For intra-observer reliability analysis, a sample of fifteen patients was re-analyzed in a period ranging from 5-7 days between first and second analysis. Intra-observer correlation coefficient and variability for LVESV were 0.980 and 1.1%, for LVEDV were 0.913 and 1.7%, respectively. For the inter-observer reliability analysis, there was a good correlation between the observers for LV volumes. The inter-observer correlation coefficient and variability for LVESV were 0.921 and 1.6%, for LVEDV were 0.876 and 2.5%.

Comparison of HRR indices and clinical parameters after CRT
Mean HRR1 (13.04 ± 5.96 vs 17.89 ± 8.94, p=0.001), HRR2 (20.47 ± 9.39 vs 23.79 ± 11.33, p=0.001) and HRR3 (25.77 ± 11.10 vs 29.20 ± 11.95, p=0.001) values improved 6 months after CRT (Figure 1). The NYHA functional capacity, MLWHFQ score, QRS duration, LVEDV, LVESV, LVEF were shown to be improved significantly at

![Figure 1](image_url)

Comparison of heart rate recovery (HRR) indices at baseline and 6 months after cardiac resynchronization therapy.
the 6th month follow-up. Comparison of echocardiographic features and exercise test parameters of the patients are presented with details in Table 2.

When study population was stratified according to echocardiographic response; Among responders mean HRR1 (13.1 ± 6.2 vs 18.7 ± 9.5, p=0.001), HRR2 (20.8 ± 9.7 vs 24.9 ± 11.9, p=0.001), HRR3 (25.8 ± 11.6 vs 29.3 ± 12.3, p=0.001), MLWHFQ score (34.2 ± 12.0 vs 25.4 ± 10.8, p=0.001) and peak exercise capacity (3.6 ± 0.9 vs 4.8 ± 1.7, p=0.001) improved 6 months after CRT.

Although there was no statistically significant improvement in MLWHFQ score and peak exercise capacity among non-responders, mean HRR1 (12.9 ± 5.6 vs 16.5 ± 8.1, p=0.001), HRR2 (19.8 ± 9.0 vs 21.8 ± 10.1, p=0.001) and HRR3 (25.7 ± 10.5 vs 28.4±11.6, p=0.016) values improved 6 months after CRT (Table 3).

Pearson’s analyses revealed a good positive correlation between LVRM and ΔHRR1 (r=0.642, p=0.001) (Figure 2). There was a moderate correlation between LVRM and ΔHRR2 (r=0.591, p=0.033) and ΔHRR3 (r=0.436, p=0.001). There was also a weak negative correlation between LVRM and Δ MLWHFQ score (r=−0.290, p=0.045).

### Table 2

Comparison of clinical, echocardiographic and exercise test parameters at baseline and six months after cardiac resynchronization therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before CRT</th>
<th>After CRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Functional Capacity</td>
<td>2.85 ± 0.58</td>
<td>1.70 ± 0.61</td>
<td>0.001</td>
</tr>
<tr>
<td>MLWHFQ score</td>
<td>36.2 ± 11.9</td>
<td>29.8 ± 12.0</td>
<td>0.001</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>147.5 ± 24.3</td>
<td>132.23 ± 17.47</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>168.19 ± 48.83</td>
<td>151.60 ± 43.2</td>
<td>0.001</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>126.65 ± 41.66</td>
<td>105.37± 37.32</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF (Simpson’s method), %</td>
<td>24.85 ± 4.12</td>
<td>30.83 ± 7.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal HR</td>
<td>72.0 ± 8.3</td>
<td>74.9 ± 9.3</td>
<td>NS</td>
</tr>
<tr>
<td>% predicted APMHR</td>
<td>75.0 ±4.5</td>
<td>76.8 ± 5.6</td>
<td>NS</td>
</tr>
<tr>
<td>HR ME, bpm</td>
<td>118.7 ± 5.8</td>
<td>121.9 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>SBP ME, mmHg</td>
<td>113.0 ± 4.2</td>
<td>114.8±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>DBP ME, mmHg</td>
<td>73.1 ± 9.6</td>
<td>71.8 ± 8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of exercise test, sec</td>
<td>307 ± 41</td>
<td>341 ± 44</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak exercise capacity, METs</td>
<td>3.6 ± 0.9</td>
<td>4.5 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>HRR1, bpm</td>
<td>13.0 ± 5.9</td>
<td>17.9 ± 8.9</td>
<td>0.001</td>
</tr>
<tr>
<td>HRR2, bpm</td>
<td>20.5 ± 9.3</td>
<td>23.8 ± 11.3</td>
<td>0.001</td>
</tr>
<tr>
<td>HRR3, bpm</td>
<td>25.7 ± 11.1</td>
<td>29.2 ± 12.0</td>
<td>0.001</td>
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</tbody>
</table>

NYHA, New York Heart Association; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; HR, heart rate; AMPHR, age predicted maximal heart rate; SBP ME, systolic blood pressure at maximal exercise; DBP ME, diastolic blood pressure at maximal exercise; METs, metabolic equivalents; HRR1–3, heart rate recovery indices (see text for full description). Numerical variables were presented as the mean ± standard deviation and categorical variables were presented as percentages.
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TABLE 3

Comparison of exercise test parameters and MLWHFQ score between responders and non-responders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n=30)</th>
<th>Non-responders (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before CRT</td>
<td>After CRT</td>
</tr>
<tr>
<td>HRR1, bpm</td>
<td>13.1 ± 6.2</td>
<td>18.7 ± 9.5†</td>
</tr>
<tr>
<td>HRR2, bpm</td>
<td>20.8 ± 9.7</td>
<td>24.9 ± 11.9†</td>
</tr>
<tr>
<td>HRR3, bpm</td>
<td>25.8 ± 11.6</td>
<td>29.3 ± 12.3†</td>
</tr>
<tr>
<td>Peak exercise capacity, METs</td>
<td>3.6 ± 0.9</td>
<td>4.8 ± 1.7†</td>
</tr>
<tr>
<td>†MLWHFQ score</td>
<td>34.2 ± 12.0</td>
<td>25.4 ± 10.8†</td>
</tr>
</tbody>
</table>

Response was defined as a reduction of end-systolic volume ≥15% at 6 months after CRT. HRR1–3, heart rate recovery indices (see text for full description); MLWHFQ, Minnesota Living With Heart Failure Questionnaire; METs, Metabolic equivalents. Numerical variables were presented as the mean ± standard deviation.

* p<0.01, † p<0.001 (by paired samples t-test or Wilcoxon signed rank test), ‡p<0.05 for comparison of basal values between responders and non-responders.

FIGURE 2

Correlation between percentage of change in exercise heart rate recovery at 1st minute (HRR1) and left ventricular reverse remodeling (decline in percentage of LVESV). r refers to correlation coefficient.
Discussion

To the best of our knowledge, our study is the first to evaluate and suggest that cardiac resynchronization therapy improves HRR in patients with symptomatic HF. The main findings of the present study are as follows: (i) CRT favorably alters the cardiac autonomic functions assessed by HRR indices, (ii) degree of improvement in HRR indices correlate with LVRM, (iii) among the all parameters, ΔHRR1 has highest correlation with LVRM, (iv) baseline HRR indices can not predict response to CRT.

With the increasing age of the population and improved survival of patients with acute coronary syndrome the incidence of HF increases (21). Approximately half of the deaths in HF are sudden and unexpected. The HF patients have 6-9 fold increased rate of sudden cardiac death compared with healthy population (21). There are several mechanisms or sequence of events responsible for sudden cardiac death in these patients (22). One of them is altered cardiac autonomic function and many clinical studies have demonstrated that certain measures of autonomic function in the setting of structural cardiovascular disease are associated with an adverse prognosis (23-24).

Cardiac resynchronization therapy (CRT) or biventricular pacing has been a major advance in long-term therapy for treatment of HF and has been shown to result in hemodynamic improvement in patients with depressed ejection fraction and intraventricular conduction delay. There are some previous studies that have assessed the effects of CRT on cardiac autonomic function (13-14,25). Fantoni et al. (13) assessed HR profile and HR variability (HRV) after CRT. They reported that CRT significantly modified the cardiac sympathetic and parasympathetic balance with a significant reduction of minimum HR, mean HR and concurrent increase of HRV indices and maximum HR after CRT in 113 HF patients. The changes of these parameters usually peaked within a few months after implantation of a new CRT device and remained stable years thereafter. Alonso et al. (25) reported that in patients with severe HF, CRT improves HRV. Improvement is preserved beyond 1 year follow-up and the favorable effect on HRV was unrelated to clinical efficacy. Sredniava et al. (26) studied the effect of CRT on HR turbulence (HRT). They found that HRT indices improved and the proportion of patients with abnormal HRT indices decreased 6 month after CRT implantation compared with before and also in responder versus non-responders. Gademan et al. (27) studied 33 HF patients and suggested that the autonomic nervous system is actively involved in CRT related LVRM. They observed that CRT acutely increased baroreflex sensitivity in responders but not in non-responders and also found CRT induced acute BRS increase has predictive value for the echocardiographic response to CRT.

HRR after graded exercise is one of the common used techniques which reflect autonomic activity (23). An attenuated HRR, which is defined as the decrease in HR immediately after exercise, reflects reduced parasympathetic nervous system (PNS) activity (28-29). Increased parasympathetic activity is protective against ischemia related dysrhythmias, and also reduces HR and blood pressure (30). Chaitman et al. (31) showed that, finding of an abnormal HRR response was a surrogate for underlying autonomic dysfunction and that the mechanism of increased mortality associated with this finding might be more related to autonomic dysfunction than to the presence or extent of coronary artery disease. HRR indices immediate-
ly after the completion of an exercise stress test were found as predictors of all cause mortality (32-33). Schwartz et al. (34) reported that increased PNS activity had been associated with a decrease in the risk of death by protecting the heart against lethal arrhythmias. Other studies have also shown that abnormal HRR, defined as failure of HR to decrease 12 beats or more during the first minute after peak exercise, independently predicted an increased mortality (7). Furthermore, Morshedi-Meibodi et al. (4) demonstrated that the greater HRR in the first minute of recovery was associated with the lower the subsequent mortality.

Our study is the first to evaluate HRR indices after CRT. Mean HRR1, HRR2 and HRR3 were improved 6 months after CRT. Interestingly, there was a significant improvement of HRR indices both in responders and non-responders. This finding suggested that favorable effect of CRT on cardiac autonomic functions was observed both in responders and non-responders which supports the findings of study performed by Alonso et al. (25). Another important finding of current study is that the degree of improvement in HRR indices correlated with LVRM. One possible explanation for this finding is that CRT decreases the permanent neurohumoral activation by decreasing the involvement of the cardiac sympathetic afferent reflex (CSAR) (27). CSAR is activated by mechanical stretch and by various metabolites, which are elevated during myocardial ischemia and with cardiac stretch (27). LVRM induced by CRT may have lowered mechanical stretch and may thus have deactivated CSAR.

Upon cessation of exercise, augmentation of parasympathetic effects on HR occurred rapidly especially within the first minute and HRR1 was a better index of autonomic function than the HRR2 and HRR3 (4,7). This may explain the highest correlation coefficient of ΔHRR1 with LVRM than the other HRR indices.

In a recent study, Thomas et al. (35) examined whether pre-implant HRR could help characterize subsequent response to CRT in 37 patients. They performed HRR following exercise only before
CRT implantation and found higher HRR indices and HR deceleration gradients (derived from HRR by using arithmetic formula) among responders. However, baseline HRR indices could not predict response to CRT in our study.

Study limitations

Limitations of the present study are the relatively small number of patients and the results are based on a single center. While this provides a theoretical limitation, it could also be considered an advantage as it ensures uniformity in data acquisition and collection. The follow-up period was limited to 6 months and long-term results were unknown.

Conclusions

CRT favorably alters the cardiac autonomic functions assessed by HRR indices. This effect of CRT on cardiac autonomic functions was observed both in responders and non-responders. However, the degree of improvement in HRR indices correlated with LVRM. There was a statistically significant correlation between improvement in HRR indices and LV remodeling. Baseline HRR indices could not predict response to CRT.

Disclosures

None

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