Impact of Exercise Training on CRP & BNP in Patients with Heart Failure with Reduced EF (HFrEF)

GHADA SELIM, M.D.; AHMED ELSHAZLY, M.D.; MOHAMED GAMAL, M.D.; MOHAMED ABDELRAHMAN, M.D. and HAZEM KHORSHID, M.D.

The Department of Cardiology, Faculty of Medicine, Ain Shams University

Abstract

Background: Brain Naturetic Peptide (BNP) and C-Reactive Protein (CRP) were found to be independently correlated to mortality and morbidity in heart failure patients. While exercise has tremendous beneficial hemodynamic and cardiovascular impact, there is, yet, a scarcity in literature data to elaborate on the impact of ET on cardiac biomarkers. Recent metanalysis of relatively small randomized trials reveal that exercise training (ET) can lower their levels significantly.

Aim of Study: This study sought to identify the impact of low-intensity exercise training on serum levels of CRP, BNP and cardiac function indices as secondary endpoints in patients with HFrEF.

Patients and Methods: Forty HFrEF patients were referred for a 3 month low-intensity exercise protocol (1-2.5 mph or 1.6-4 km/hr, 0% grade) guided by Borg scale (11-13) at Ain Shams cardiac rehabilitation program in the period between October, 2013 and January, 2015. Exercise training was monitored by patients' tolerance, ECG and BP response. A full echocardiography and blood levels of BNP and CRP were obtained before and after completing the program.

Results: Exercise training significantly reduced BNP levels but had non-significant impact on CRP (238.00 ± 123.687 vs. 161.68 ± 79.567pg/ml, p-value <0.001) and (5.61 ± 1.98 vs. 4.86±2.37mg/ml, p-value=0.128) respectively. LVEF significantly improved and LV reverse remodeling was observed in 8 patients (20% of patients) by the end of the exercise training program. Right ventricular PW tissue Doppler-derived peak systolic (RV-s’) and Tricuspid Annular Plane Systolic Excursion TAPSE showed significant improvement (11.93 ± 2.505 vs 12.15±2.558cm/s, p-value <0.001) and (19.40±3.973 vs. 19.80±4.071, p=0.005) respectively.

Conclusion: In patients with HFrEF, low-intensity exercise training program significantly improved BNP levels, but had a non-significant effect on CRP levels. The echocardiographic determinants of systolic and diastolic functions significantly improved.

Key Words: Cardiac rehabilitation – Biochemical Markers – Exercise Training – HFrEF.

Introduction

Despite recent advances in pharmacological and device therapy for heart failure patients, quality of life and survival rates remain unsatisfactory [1]. Exercise training (ET) has been accepted as Class B level of evidence for patients with HFrEF, due to its beneficial impact on exercise tolerance and quality of life [2]. Additionally, large trials such as HF-ACTION showed that ET adjuvant to medical treatment had a hospitalization and mortality benefit compared to standard medical treatment alone [8], while other metaanalysis demonstrated that ET ≥6 months could reverse LV remodelling in heart failure patients [3].

Biomarkers such as CRP and BNP are objective measurable substances that respond to pharmacological interventions and were found to be independently related to morbidity and mortality in patients with HFrEF [4]. Their testing has therefore been recommended by the European Society of Cardiology as part of risk-stratification of this patient cohort [8]. Little literature exists about the effect of ET on cardiac biomarkers.

Aim of the work: We sought to identify the effect of low-intensity exercise on CRP, BNP as well as echocardiographic determinants of cardiac function in HFrEF patients.

Patients and Methods

Patient Selection: This is a prospective single-center study. Forty patients with LV systolic dysfunction (LVEF <40%) were referred for cardiac rehabilitation program at Ain Shams University Hospital. They were on optimal treatment for heart failure (for at least one month) including diuretics, maximal tolerable doses of RAAS inhibitors (ACEI, ARBs and aldosterone antagonists and BB according to recommendations of the European Society of Cardiology guidelines for treatment of HF.
(2012). We excluded patients with any of the following: NYHA class IV, acute coronary syndrome, end stage HF due to valvular HD, patients who had incapacitating, advanced or terminal medical illness, patients with recent acute medical condition (such as stroke, TIA, myocarditis), patients with contraindication to exercise, patients with CRT or ICD, patients who were referred for CABG and patients who did not attend at least 80% of the exercise sessions.

Methodology: Patients were recruited from Ain Shams Cardiology Department during the period between October, 2013 and January, 2015. Detailed history was taken including heart failure etiology, NYHA class and risk factors. Patients were on maximal tolerated doses of guideline-directed medical treatment for heart failure. Thorough physical examination was performed including vital sign, heart failure signs and cardiac murmurs. Twelve lead ECG was conducted.

A 2 dimensional echocardiography images were averaged from ≥3 consecutive cardiac cycles or ≥5 cycles in AF with standard views (4-chamber, 2-chamber, and long-axis). LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were obtained using modified biplane Simpson's method. A reduction in LVEVF of ≥10% was used as the cutoff value to define patients with LV reverse remodeling. Left atrial volume was calculated by the prolate ellipse method. The apical 4-chamber view was used to derive PWD transmitral flow profile, pulmonary venous flow and color tissue doppler-derived mitral annular velocity. The mitral flow early diastolic wave velocity (E), late diastolic atrial contraction wave velocity (A), and the E-wave deceleration time (E-DcT) were measured. The pulsed wave Doppler-derived pulmonary venous systolic wave velocity (PV-S), early diastolic wave velocity (PV-D), atrial contraction reverse wave velocity (PV-Ar), and the D-wave deceleration time (PV D-DcT), were also measured. Spectral pulsed-wave tissue Doppler-derived peak systolic velocity (s'), early diastolic velocity (e'), late diastolic velocity (a'), as well as isovolumetric contraction velocity (IVV), were obtained from the septal, and lateral mitral annulus and the E/e' ratio was measured to estimate the LV filling pressure for all patients. Tricuspid annular plane systolic excursion (TAPSE) measurement was obtained from an apical four-chamber ultrasound view, placing the M-mode line at the lateral tricuspid valve annulus (at the attachment of the valve leaflet to the right ventricular wall) with M-mode tracing and measuring the height of the annulus movement during systole.

Venous blood sampling & assay for sCRP and BNP were performed using standard venipuncture techniques. The technique employs monoclonal antibody directed against a specific antigen on the CRP/hs CRP molecule. Specimens were taken within an hour of sampling, frozen at –20 C for up to six months.

Exercise training program: After explaining the program to the patients and obtaining their written consent, patients were enrolled in a low-intensity exercise program twice/week for 3 months using treadmill machine. They exercised at Borg scale (11-13) (1-2.5 mph or 1.6-4 km/hr, 0% grade). Exercise training was monitored by patients' tolerance and development of symptoms, ECG and BP response. Special considerations were taken: Exercise was re-scheduled if patient presented with fever, tachycardia or uncontrolled blood pressure. Exercise session was terminated if the patient's SBP dropped >10mmHg, developed arrhythmias, severe dyspnea or chest pain on a low workload, or if clinical examination showed de novo congestion. Blood sugar levels were tested before and after exercise sessions and if blood sugar was <100mg/dL exercise was delayed 15min and patients were given 15g of carbohydrate. If blood sugar was >300mg/dL, patients may exercise if they were asymptomatic, optimally hydrated, and showed negative ketones in blood +/- urine; otherwise, patient's exercise session would be rescheduled after blood sugar was controlled. After program completion, patients' serum levels of BNP, CRP were reassessed and echocardiography repeated.

Statistical analysis: Measured data were described as range, mean and standard deviation (for numerical parametric data) and range, median and interquartile range (for numerical non-parametric data). The independent sample t-test, ANOVA were used. Linear regression was expressed as Pearson correlation coefficients. For analysis of the independent determinants we used multivariate linear and logistic regression analysis. A p-value <0.05 was statistically significant.

Table (1): Demographic and clinical data.

| Age (yrs) | 56.2±9.4 |
| Sex (m/f) | 27 (82.5%)/7 (17.5%) |
| BMI* (kg/m²) | 27±2.9 |
| Hypertension** (%) | 32 (80%) |
| Diabetics# (%) | 24 (60%) |
| Smoker/ex-smoker (%) | 15 (37%)/15 (37%) |

*BMI: Body Mass Index (>30kg/m²); ** Hypertension (>140/90); # DM (HbA1c >6.5%)
Table (2) summarizes the treadmill exercise training variables in the study group, which started the program with exercise duration of 15 min and speed 1.5 km/hour, which was significantly increased at the end of the program to duration of 26.38 ± 5.309 min and speed 3.050 ± 0.5639 km/hour (p-value <0.001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>At the start</th>
<th>At the end</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed (km/hr)</td>
<td>1.5 ±.000</td>
<td>3.050 ±.5639</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>15.00 ±.000</td>
<td>26.38 ±5.309</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Effect of exercise training on clinical and laboratory parameters:

Table (3) demonstrates the clinical and laboratory parameters before and after completing the exercise training program. After completing the program, there was a significant reduction in heart rate (91.78 ± 8.393 vs. 76.98 ± 7.790) bpm (p-value <0.001), mean blood pressure (123.70 ± 17.081 vs. 108.73 ± 13.519) mmHg (p-value <0.001), exercise tolerance (3 patients with NYHA I vs. 34 patients); (p-value <0.001), and BNP level (238.00 ± 123.687 vs. 161.68 ± 79.567) pg/ml (p-value <0.001). There was a non-significant change in the sCRP level, (5.61 ± 1.98 vs. 4.86 ± 2.37) mg/ml, p-value=0.128.

Table (3): Pre- and Post- exercise training data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-exercise</th>
<th>Post-exercise</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Heart rate (bpm)</td>
<td>91.78 ± 8.393</td>
<td>76.98 ± 7.790</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>123.70 ± 17.081</td>
<td>108.73 ± 13.519</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA* (I/II/III/IV)</td>
<td>3/ 29/ 8/ 0</td>
<td>34/ 6/ 0/ 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP** (pg/ml)</td>
<td>238.00 ± 123.687</td>
<td>161.68 ± 79.567</td>
<td>0.002</td>
</tr>
<tr>
<td>CRP*** (mg/ml)</td>
<td>5.61 ± 1.98</td>
<td>4.86 ± 2.37</td>
<td>0.128</td>
</tr>
</tbody>
</table>

**Brain Natriuretic Peptide.
***C-Reactive Protein.

Echocardiographic chamber quantification before starting and after completing the program:

Post-exercise training, the mean LVEDVI (77.8 ± 20.4 vs. 76.4 ± 20) ml/m²; (p-value=0.836), mean LVESVI (53.6 ± 15 vs. 49.6 ± 14.8) ml/m²; (p-value=0.235) and LAVI (35.4 ± 13 vs. 33.8 ± 12.5) ml/m² (p-value=0.558) did not show significant improvement, unlike the left ventricular EF which significantly improved (31.65 ± 4.633 vs. 35.25 ± 5.251, p-value=0.002) and LV reverse remodeling was observed in 8 patients (20%) of patients.

Table (4): Pre- and Post- Exercise training echocardiographic LV measurements.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-exercise</th>
<th>Post-exercise</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDVI* (ml/m²)</td>
<td>77.8 ± 20.4</td>
<td>76.4 ± 20</td>
<td>0.836</td>
</tr>
<tr>
<td>LVESVI** (ml/m²)</td>
<td>53.6 ± 15</td>
<td>49.6 ± 14.8</td>
<td>0.235</td>
</tr>
<tr>
<td>EF# (%)</td>
<td>31.65 ± 4.633</td>
<td>35.25 ± 5.251</td>
<td>0.002</td>
</tr>
<tr>
<td>LAVI* (ml/m²)</td>
<td>35.4 ± 13</td>
<td>33.8 ± 12.5</td>
<td>0.558</td>
</tr>
</tbody>
</table>

*LVEDVI: Left Ventricular End Diastolic Volume Index.
**LVESVI: Left Ventricular End Systolic Volume Index.
#EF: Ejection Fraction.
*LAVI: Left Atrial Volume Index

Doppler Echocardiographic determinants of LV Diastolic function before starting and after finishing the program:

After completing the exercise training program the trans mitral PWD early diastolic E wave velocity (85.18 ± 20.585 vs. 80.88 ± 19.135 cm/s, p-value=0.336), A wave velocity (67.33 ± 29.721 vs. 64.65 ± 27.494 cm/s, p-value=0.677), pulmonary venous systolic wave velocity (PV-S), early diastolic wave velocity (PV-D), atrial contraction reverse wave velocity (PV-Ar), and the D-wave deceleration time (PV-D-DcT) showed non-significant changes. However, Spectral pulsed-wave tissue Doppler-derived early diastolic velocity (e’) (6.09 ± 1.601 vs. 6.98 ± 1.459 cm/s, p-value=0.011) and E/e’ (14.670 ± 6.0942 vs. 11.925 ± 4.2223, p=0.022) showed significant changes (Table 5).

Table (5): Pre-and Post- exercise training echo- determinants of LV diastolic function.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-exercise</th>
<th>Post-exercise</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E* (cm/s)</td>
<td>85.18 ± 20.585</td>
<td>80.88 ± 19.135</td>
<td>0.336</td>
</tr>
<tr>
<td>E-DcT** (msec)</td>
<td>159.78 ± 69.377</td>
<td>163.65 ± 58.951</td>
<td>0.788</td>
</tr>
<tr>
<td>A*** (cm/s)</td>
<td>67.33 ± 29.721</td>
<td>64.65 ± 27.494</td>
<td>0.677</td>
</tr>
<tr>
<td>E/A#</td>
<td>1.585 ± 1.0477</td>
<td>1.506 ± 0.8647</td>
<td>0.713</td>
</tr>
<tr>
<td>E’## (cm/s)</td>
<td>6.09 ± 1.601</td>
<td>6.98 ± 1.459</td>
<td>0.011</td>
</tr>
<tr>
<td>A’## (cm/s)</td>
<td>6.30 ± 1.757</td>
<td>6.30 ± 1.698</td>
<td>1.000</td>
</tr>
<tr>
<td>E/E’##</td>
<td>14.670 ± 6.0942</td>
<td>11.925 ± 4.2223</td>
<td>0.022</td>
</tr>
<tr>
<td>PV-S^*** (cm/s)</td>
<td>46.13 ± 9.129</td>
<td>44.95 ± 8.268</td>
<td>0.559</td>
</tr>
<tr>
<td>PV-D^### (cm/s)</td>
<td>66.58 ± 13.83</td>
<td>64.90 ± 11.98</td>
<td>0.560</td>
</tr>
<tr>
<td>PV-Ar^** (cm/s)</td>
<td>39.18 ± 32.925</td>
<td>36.33 ± 31.703</td>
<td>0.694</td>
</tr>
<tr>
<td>PV-S/D^**</td>
<td>0.74 ± 0.39</td>
<td>0.73 ± 0.36</td>
<td>0.911</td>
</tr>
<tr>
<td>PV-D-DcT^#</td>
<td>247.85 ± 58.774</td>
<td>233.35 ± 46.038</td>
<td>0.223</td>
</tr>
</tbody>
</table>

*E: Early Filling.
**E-DcT: E-Deceleration Time.
***A: Late atrial Filling.
#E/A: Ratio between Early Filling and Late Atrial Filling by Doppler.
##E’: Early Filling by Tissue Doppler.
#A’: Late Atrial Filling by Tissue Doppler.
*E/E’: Ratio between Early Filling Phase measured by Doppler echocardiography and Early Filling Phase measured by Tissue Doppler.
**PV-S: Pulmonary Vein Velocity in Systole.
###PVD: Pulmonary Vein velocity in Diastole.
*PV-Ar: Pulmonary Vein Velocity in Atrial Reverse.
**PV-S/D: The ratio between Pulmonary Vein Velocity in Systole/Diastole.
*PVD-DcT: Deceleration Time of the Pulmonary Vein Velocity in Diastole.
Pre-and post-echocardiographic indicators of RV Systolic function:

After completing the exercise training program the right ventricular PW tissue Doppler-derived peak systolic (RV-s') (11.93±2.505 vs 12.15±2.558 cm/s, p-value < 0.001) and Tricuspid Annular Plane Systolic Excursion TAPSE (19.40±3.973 vs. 19.80±4.071, p=0.005) showed significant improvement (Table 6).

Table (6): Echocardiographic determinants of RV Systolic function before starting and after finishing the program.

<table>
<thead>
<tr>
<th></th>
<th>Pre-exercise</th>
<th>Post-exercise</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV-s' (cm/s)</td>
<td>11.93±2.505</td>
<td>12.15±2.558</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>19.40±3.973</td>
<td>19.80±4.071</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Discussion

Impact of exercise training on sympatho-vagal balance and resting heart rate:

Physical exercise is known to significantly reduce muscle sympathetic activity, circulating catechol amines, enhances vagal tone, and baroreceptor sensitivity [12,13]. Furthermore, it increases endothelium-dependent vasodilation, reduces sympathetic discharge, thus normalizes the autonomic balance [14,15]. Our results show a similar reduction in resting heart rate (91.78±8.393 vs. 76.98±7.790 bpm) that was significant (p-value <0.001), which came in agreement with several studies [16,17].

Effect of training on exercise tolerance:

Exercise improves muscular strength, endurance and oxygen saturation [18]. Our study shows that exercise improved the exercise tolerance in HFrEF patients as evidenced by the improvement in NYHA class [3 patients only (7.5%) at the beginning of exercise program with NYHA I vs. 34 (85%) by the end of exercise program (p-value <0.001)]. This agrees with Erbs et al., who studied 37 patients with HF (NYHA class III) who exercised for six months, and reported average functional improvement of one NYHA class compared to control group [19].

Effect of the training program on cardiac function:

1- Effect on LV volumes and EF:

In this study completion of the exercise training program did not yield a significant improvement in the mean LVEDVI or the mean LVESVI compared to baseline values. This was concordant with Dubach et al., who found no changes in LVEDVI or LVESVI [20].

On the other hand, LVEF significantly improved which agrees with Mehani et al., [21] who reported significant of ejection fraction with exercise training (33.09±4.77% to 48.93±8.38%; p<0.001) vs no improvement in control group (35.8±6.87% to 37.27±7.82%; p=NS). Interestingly this is not concordant with Dubach et al., who reported that no difference was observed in EF (38.0±9 pre and 38.2±10% post) vs (37.0±10 pre and 38.3±13% post) in the exercise and control group respectively [20]. This contradiction may be due to difference in the study group enrolled in Dubach et al. (post anteroseptal or inferolateral myocardial infarction), exercise training program design (which was high-intensity program), difference in the investigative tool used for assessment (MRI) and finally the shorter follow-up period (2 months in Dubach et al.) [20].

Finally, data from ELVD-CHF, a multi-centered RCT that included HFrEF (mean EF, 25.3 ±4%) reported that 6-month training had a reverse-remodeling effect on LVEDVI and LVESVI with significant improvement in EF (LVEDV, from 142±26 to 135±26mL/m², p<0.006, LVESV, from 107±24 to 97±24mL/m², p<0.05), Ejection fraction improved by 16% in the training group (p<0.01) but not in the control group [22].

2- Effect on LV diastolic function:

The PW TDI early diastolic velocity (e') (6.09±1.601 vs. 6.98±1.459cm/s, p-value=0.111) and E/e' (14.670±6.0942 vs. 11.925±4.2223, p-value=0.022) showed a significant improvement. This is concordant with Sandri et al., who studied the impact of endurance exercise on LV diastolic function in two age groups (under 55 years and above 65 years) and found that endurance training improved LV diastolic function in HFrEF patients irrespective of their age [22].

Effect of exercise on BNP & CRP:

BNP/NT-proBNP are released entirely from cardiac tissue, and are therefore reflective of wall stress, volumes and filling pressure [24]. Elevated plasma levels of BNP and CRP are linked with augmented risk of negative outcomes in HF patients [30]. Since Exercise training improves hemodynamics, it is assumed a reduction in naturetic peptide would result.

In this study, completing an exercise program led to a significant reduction in BNP level. This is concordant with Sarullo et al., [26] who found that NT pro-BNP levels declined from (3376±313 to 1434±1673) pg/ml, p:0.043. Exercise was also associated with NYHA class improvement. Fur-
thermore, NA Smart et al., [27] who reviewed nine RCTs with 463 patients diagnosed with heart failure (NYHA class ranging from I to III) and reported a significantly positive influence of exercise on BNP (−79pg/mL, 95% CI −141 to −17, I² = 73% -five studies) and NT-pro-BNP (−621pg/mL, 95% CI −844 to −398, I² = 75% - six studies).

Additionally, Malandish et al., [28] conducted a meta-analysis of 28 articles including 2563 participants with exercise: 1350 vs control: 1213 to study the impact of exercise on the NT-proBNP and BNP levels in HF patients. They found that NT-proBNP marker was significantly reduced [-0.22 (SMD and 95% CI : 0.386 to −0.071), p <0.005].

Similarly, Lv D [29] conducted a wide search on the effect of exercisetrainingon myocardial function in HF patients and metaanalysis of 9 articles (752 patients) revealed that exercise training had a significantly impacted cardiac function indices (LVEF, CRP and BNP) in HF patients (p<0.05).

On the other hand it was not concordant with Nilson et al., [30] who did not find significant changes in NT pro-BNP levels 12 months post moderate-intensity exercise, in 78 patients with stable HF (mean EF 30±8.6%) despite an improvement in functional capacity that was significant. This may be due to the older age group (70±8 years in Nilson et al. vs. 56.2±9.4 in our study).

Study Limitations:
A single medical center with small number of patients predominantly male gender. Cardiovascular morbidity, mortality and cost-effectiveness could not be determined.

Conclusion:
Low intensity aerobic exercise training program not only improves functional capacity and hemodynamics but also improves many echocardiographic determinants of cardiac functions and BNP level in patients with HFrF.

References


تأثير التدريبات الرياضية على CRP والBNP في مرضى ضعف عضلة القلب

أجريت هذه الدراسة لتحقيق تأثير التدريبات الرياضية منخفضة الشدة على العلامات البيوكيميائية ومحدودات الوظائف الانتقائية والإنبساطية للقلب بالموجبات الصوتية لدى مرضى ضعف عضلة القلب. 

أجريت الدراسة الحالية على 40 مريضاً من جميع الفئات العمرية ومن كلا الجنسين، تحت إشرافهم إلى مستشفى جامعة عين شمس برنامج إعادة التأهيل القلبي خلال الفترة ما بين أكتوبر 2013 ويناير 2015. كانوا يتلقون العلاج الطبي الأمثل لضعف عضلة القلب (مدة شهر على الأقل).

كان لدى جميع المرضى تاريخ كامل وفحص جسدي شامل، ثم سحب عينات دم لتحليل CRP والBNP، وعمل رسم قلب 12 وأشعة صوتية على القلب قبل وبعد البرنامج الرياضي الذي استمر لمدة 3 أشهر.

وقد تحسن هام إحصائياً في مستوى BNP في الدم، لم يكن هناك تغيير معتمد به إحصائياً في مستوى CRP. كانت هذه النتائج متوافقة مع معظم الدراسات السابقة حول هذا الموضوع.

وقد ارتبط أيضاً تحسناً إحصائياً مهماً في العديد من محدودات الوظيفة الانتقائية والإنبساطية للقلب، كما لوحظ التشكل العكسي لضعفة القلب في 20% من المرضى في مجموعة الدراسة.