Ischaemic aetiology predicts exercise dyssynchrony in patients with heart failure with reduced ejection fraction

Jakub Stępniewski, Grzegorz Kopeć, Wojciech Mańgoń, Piotr Podolec

Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland

Abstract

Background: Left ventricular (LV) dyssynchrony is common in patients with heart failure with reduced ejection fraction (HFrEF). However, various conditions, including exercise, may affect its presence. LV dyssynchrony at exercise (ExDYS) has been associated with lower cardiac performance and exercise capacity but with higher cardiac resynchronisation therapy (CRT) response. Therefore, understanding the mechanisms underlying ExDYS may improve patient selection for CRT.

Aim: We sought to identify predictors of ExDYS among patients with HFrEF and prolonged QRS duration.

Methods: Consecutive patients with stable chronic heart failure, LV ejection fraction (LVEF) < 35%, sinus rhythm, and QRS ≥ 120 ms were eligible. Two-dimensional echocardiography and tissue-Doppler were performed at rest and during peak cyclo-ergometer exercise to assess LV systolic (LVEF) and diastolic functions (mitral E-to-e’-wave velocities [E/e’]) and dyssynchrony. Dyssynchrony was defined as a maximal difference between time-to-peak systolic velocities of ≥ 65 ms from opposing basal segments.

Results: We included 48 patients (aged 63.7 ± 12.2 years, 81.3% male). Ischaemic aetiology (ischaemic cardiomyopathy [ICM]) was present in 23 (47.9%) patients. Dyssynchrony at rest (rDYS) was present in 32 (66.6%) patients, while ExDYS was seen in 23 (47.9%). ExDYS correlated with ICM, lower LVEF, and higher E/e’ ratio. ICM remained a significant predictor of ExDYS in multiple regression model (odds ratio [OR] 4.3, 95% confidence interval [CI] 1.2–15.7, p = 0.03). On exercise, 19 (39.5%) patients changed the rDYS status. Although exercise-induced dyssynchronisation was observed only in ICM patients, exercise-induced resynchronisation was more likely in patients with lower rest E/e’ ratio (OR 0.85, 95% CI 0.75–0.97, p = 0.02).

Conclusions: Ischaemic aetiology of HFrEF is an important predictor of ExDYS. Restoration of LV synchronicity during exercise is more likely in patients with less advanced LV diastolic dysfunction.

Key words: stress echocardiography, dilated cardiomyopathy, QRS prolongation, cardiac resynchronisation therapy, left bundle branch block

INTRODUCTION

In most recent studies, the presence of left ventricular (LV) dyssynchrony at exercise was shown to predict lower cardiac performance and exercise capacity in patients with heart failure with reduced ejection fraction (HFrEF) [1, 2]. Interestingly, patients with exercise dyssynchrony were also more likely to respond to cardiac resynchronisation therapy (CRT) [3]. Therefore, understanding the mechanisms behind exercise-related dyssynchrony may improve patient selection for CRT.

In the present study, we aimed to identify predictors of exercise dyssynchrony among patients with HFrEF and prolonged QRS duration.

METHODS

Study population

We prospectively enrolled consecutive HF patients who were considered for CRT device implantation at the John Paul II Hospital in Krakow, Poland in 2013 and 2014. Inclusion criteria comprised the following: (1) New York Heart Association (NYHA) functional class II–IV despite optimal medical therapy and optimal coronary revascularisation; (2) LV ejection fraction (LVEF) ≤ 35% and QRS duration ≥ 120 ms on 12-lead electrocardiogram; and (3) sinus rhythm and no exacerbations within the past three months. Heart failure (HF) of ischaemic aetiology (ischaemic cardiomyopathy [ICM]) was diagnosed...
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Exercise stress echocardiography

Following the examination at rest, exercise echocardiography was performed on cycle ergometer (Ergoline 9000 Ergoline GmbH, Bitz, Germany) in semi-recumbent position with increasing workload. The initial workload was 20 W and was raised every 2 min by additional 20 W. The tests were terminated on patient’s request after achieving maximal effort. Echocardiographic recordings were done continuously throughout the exercise and stored digitally for subsequent off-line analysis on EchoPAC GE medical software. Peak exercise measurements were obtained from the final 2-min cycle. Each measurement was derived from at least three heart beats and expressed as the mean. No changes to patients’ pharmacotherapy were made for the sole purpose of the stress test.

Dyssynchrony evaluation

Time-velocity curves of six basal segments were used to assess LV dyssynchrony at rest (rDYS) and at peak exercise (ExDYS). Time-to-peak systolic velocity (Ts) was measured from the onset of the QRS complex to the peak myocardial systolic velocity in each of the six basal segments. The differences between Ts of opposing wall segments were calculated to determine opposing wall delays. At least one opposing wall delay (maxTsD) ≥ 65 ms was indicative of rDYS and ExDYS. Ts was corrected for the RR interval using the Bazett formula.

Statistical analysis

Categorical variables were described as counts and percentages, and continuous variables as means ± standard deviation or median and interquartile range. We used the unpaired Student t test for normally distributed variables, the Mann-Whitney U test for non-normally distributed continuous data, and the χ² test for categorical data to compare patients with and without ExDYS. In order to test the significance level of rest and peak exercise differences, we used the paired Student t test and the Wilcoxon test.

We used univariate logistic regression analysis to evaluate the association between the presence of ExDYS and its potential predictors, including age, sex (0 — male, 1 — female), HF aetiology (0 — DCM, 1 — ICM), QRS duration and morphology (0 — non-specific intraventricular conduction delay [IVCD], 1 — left bundle branch block [LBBB]), LV end-diastolic volume index (LVEDV index), markers of LV systolic and diastolic functions (LVEF and E/e’ ratio, respectively), and the presence of rDYS. Similarly, using univariate logistic regression models we investigated the association between exercise-induced changes of rDYS status, including exercise-induced resynchronisation, and exercise-induced dysynchronisation and its potential predictors including age, sex (0 — male, 1 — female), HF aetiology (0 — DCM, 1 — ICM), QRS duration and morphology (0 — IVCD, 1 — LBBB), LVEDV index, E/e’.

if a patient had a history of myocardial infarction, coronary revascularisation, or had angiographically significant stenotic lesions of > 50% in coronary arteries, and a diagnosis of non-ischaemic HF (dilated cardiomyopathy [DCM]) was made when there was no history of coronary artery disease. Patients with a history of any cardiac implantable electronic devices, persistent atrial fibrillation, or significant respiratory, neurological, or orthopaedic disorder precluding cycle ergometer exercise were excluded from the study.

All patients provided their written, informed consent to participate in this study. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Committee at the Jagiellonian University in Krakow, Poland (KBET/110/B/2013).

All measurements and patients’ medical records were prospectively obtained by the authors themselves.

Echocardiography

All echocardiographic examinations were performed with the use of a commercially available Vivid 7 device (GE Medical System, Horten, Norway) equipped with a phased array 3.5-MHz transducer and tissue Doppler imaging (TDI) software. The images were stored digitally for offline analysis on EchoPac software (GE Vingmed, Horten, Norway). Conventional M-mode, two-dimensional (2D), and Doppler parameters were calculated. TDI data were recorded in apical four-, two-, and three-chamber views with sector size and depth optimisation for the highest frame rate. Regional time-velocity curves were produced offline from the stored TDI colour images by placing sample volumes over six basal LV segments. All measurements were performed by an experienced echocardiographer by averaging three or more consecutive heart beats.

Left ventricular volumes and LVEF, as a measure of LV systolic function, were calculated with 2D-echocardiography from apical four- and two-chamber views, using the biplane disc summation method [4], and similarly for left atrial volume (LAV). Chamber volumes were normalised for body surface area.

Calculation of the E/e’ ratio, adopted as a measure of LV diastolic function, was performed by dividing peak mitral E-wave velocity acquired with pulsed-wave Doppler by TDI-derived pulsed-wave, mean septal, and lateral mitral annulus early diastolic velocities (e’).

A conventional 16-segment LV model was used to characterise regional contractility of the LV walls by scoring each segment from one to four on the basis of systolic thickening and motion [4]. Wall motion score index (WMSI) was calculated as the sum of all scores divided by the number of segments visualised. Contractile reserve (CR) was defined as a decrease of WMSI by at least 0.20 from rest to peak exercise.

The severity of mitral regurgitation (MR) was evaluated qualitatively and graded from I (mild) to IV (severe).
and markers of LV systolic and diastolic functions (LVEF and E/e’ ratio, respectively). Multiple stepwise logistic regression analysis was used to evaluate the associations between the presence of ExDYS or exercise-induced changes of rDYS status and their potential predictors. In these models we used only those potential predictors which were significantly associated with ExDYS or exercise-induced changes of rDYS status in univariate models.

The significance level was set at p-value < 0.05. Statistical analyses were performed with Statistica PL software (version 12, StatSoft, Inc., Krakow, Poland) and MedCalc version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium).

**RESULTS**

**Patients’ characteristics**

There were 54 patients eligible for the study, of whom six were excluded due to insufficient quality of echocardiographic recordings. Among 48 enrolled patients aged 63.7 ± 12.2 years, men represented the majority (39; 81.3%). ICM was present in 23 (47.9%) patients, and DCM in 25 (52.1%). Thirty (62.5%) patients were in NYHA class III, 12 (25%) in class II, and six (12.5%) in class IV. Median N-terminal pro-B-type natriuretic peptide level was 1667 pg/mL (503–3309 pg/mL). Median QRS duration was 150 ms (120–160 ms) with the LBBB morphology present in 28 (58.3%) patients and non-specific intraventricular conduction disturbances found in 20 (41.7%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 48)</th>
<th>Without ExDYS (n = 25)</th>
<th>With ExDYS (n = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>63.7 ± 12.2</td>
<td>64 ± 11.7</td>
<td>63.3 ± 12.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Women/men</td>
<td>9 (18.7)/39 (81.3)</td>
<td>6 (24)/19 (76)</td>
<td>3 (13)/20 (87)</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI [kg/m^2]</td>
<td>26.5 ± 3.8</td>
<td>26.6 ± 4.3</td>
<td>26.3 ± 3.3</td>
<td>0.78</td>
</tr>
<tr>
<td>Ischaemic/non-ischaemic HF</td>
<td>23 (47.9)/25 (52.1)</td>
<td>8 (32)/17 (68)</td>
<td>15 (65.2)/8 (34.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>NYHA class:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (25)</td>
<td>6 (24)</td>
<td>6 (26.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>III</td>
<td>30 (62.5)</td>
<td>18 (72)</td>
<td>12 (52.2)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6 (12.5)</td>
<td>1 (4)</td>
<td>5 (21.7)</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP [pg/mL]</td>
<td>1667 (503–3309)</td>
<td>1460 (628–2616)</td>
<td>2009 (491–5306)</td>
<td>0.22</td>
</tr>
<tr>
<td>HR [bpm]</td>
<td>70.6 ± 8.9</td>
<td>71.1 ± 9.4</td>
<td>70.1 ± 8.5</td>
<td>0.7</td>
</tr>
<tr>
<td>QRS duration [ms]:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120–129 ms</td>
<td>13 (27)</td>
<td>8 (61)</td>
<td>5 (39)</td>
<td></td>
</tr>
<tr>
<td>130–149 ms</td>
<td>11 (23)</td>
<td>6 (55)</td>
<td>5 (45)</td>
<td></td>
</tr>
<tr>
<td>≥ 150 ms</td>
<td>24 (50)</td>
<td>11 (46)</td>
<td>13 (54)</td>
<td></td>
</tr>
<tr>
<td>LBBB/IVCD</td>
<td>28 (58.3)/20 (41.7)</td>
<td>13 (52)/12 (48)</td>
<td>15 (65.2)/8 (34.8)</td>
<td>0.52</td>
</tr>
<tr>
<td>β-blocker</td>
<td>47 (97.9)</td>
<td>24 (96)</td>
<td>23 (100)</td>
<td>0.96</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>47 (97.9)</td>
<td>24 (96)</td>
<td>23 (100)</td>
<td>0.96</td>
</tr>
<tr>
<td>ARA</td>
<td>44 (91.6)</td>
<td>22 (88)</td>
<td>22 (95.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>44 (91.6)</td>
<td>23 (92)</td>
<td>21 (91.3)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

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**Rest and stress echocardiography**

Rest and stress echocardiographic examinations were completed successfully, with no significant adverse events. Stress examinations were terminated at a mean workload of 76.2 ± 30.5 W. Detailed rest and exercise echocardiographic parameters are presented in Table 2. Left heart chambers were enlarged with a median LVEDV_index of 169 mL/m² (131–194 mL/m²) and a mean LAV_index of 66.7 ± 25.9 mL/m². Global and regional LV systolic functions were decreased with a mean LVEF of 23.6% ± 6% and a mean WMMSI of 2.18 ± 0.38. Diastolic LV function was impaired with mean E/e’ ratio of 17.1 ± 8.

Exercise resulted in a decrease in mean E/e’ ratio as compared to rest values (14.7 ± 6.2, p = 0.03). In contrast,
mean LVEF (24.4% ± 7.0%, p = 0.23) remained without significant changes. Mean peak exercise WMSI was lower as compared to the value at rest (2.07 ± 0.36, p < 0.001) and reduced by at least 0.20 at peak exercise in 16 (33.3%) patients, revealing CR.

**Dyssynchrony**

The mean value of maxTsD was 85.4 ± 41.2 ms at rest and 76.4 ± 42.8 ms at peak exercise (p = 0.15). rDYS was identified in 32 (66.6%) patients, and ExDYS in 23 (47.9%). Two-thirds (15 [65.2%]) of patients with ExDYS had ICM as compared to patients without ExDYS, in whom the majority had DCM (17 [68%]; p = 0.04; Table 1). Patients with ExDYS as compared to patients without ExDYS had lower mean LVEF and higher mean E/e’ ratio (Table 2). No differences in the presence of rDYS were observed between those with or without ExDYS (18 [78.3%] vs. 14 [56%], p = 0.18). The WMSI was similar in both groups (2.3 ± 0.23 vs. 2.1 ± 0.46, p = 0.06, with and without ExDYS, respectively) and it increased in a similar way during exercise in patients with and without ExDYS, irrespective of HF aetiology. The CR was equally prevalent in patients with and without ExDYS (8 [34.7%] vs. 8 [32%], p = 0.91).

Univariate logistic regression analysis showed that the presence of ExDYS correlated with ICM (odds ratio [OR] 4; 95% confidence interval [CI] 1.2–13.2; p = 0.02), lower LVEF (OR 0.88; 95% CI 0.78–0.98; p = 0.02), and higher E/e’ ratio (OR 1.11; 95% CI 1.01–1.2; p = 0.02; Table 3). No associations were found between the presence of ExDYS and age, sex, QRS duration, presence of LBBB, LVEDV index, or the presence of rDYS. In the multiple stepwise regression model, ICM remained an important predictor of ExDYS (OR 4.3; 95% CI 1.2–15.7; p = 0.03). In patients with ICM the presence of ExDYS correlated with a higher E/e’ ratio (OR 1.2; 95% CI 1.1–1.4; p = 0.006).

Exercise resulted in a change of rDYS status in 19 (39.5%) patients (Fig. 1, 2). Fourteen (73.7%) regained LV synchronicity, whereas five (26.3%) became dyssynchronous. All five patients who became dyssynchronous at peak exercise had ICM. Among patients who resynchronised at peak exercise, 11 (78.6%) had DCM and three (21.4%) had ICM (p = 0.11). Exercise-induced resynchronisation was associated with a lower rest E/e’ ratio (OR 0.85; 95% CI 0.75–0.97; p = 0.02) and a lower peak exercise E/e’ ratio (OR 0.87; 95% CI 0.75–0.99; p = 0.049) (Table 4). The rest E/e’ ratio remained an important predictor of exercise-induced re-synchronisation in the multiple stepwise regression model (OR 0.85; 95% CI 0.75–0.97; p = 0.02). No associations were found between exercise-induced dyssynchronisation and its potential predictors.

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**Table 2. Echocardiographic parameters at rest and at peak exercise**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 48)</th>
<th>Without ExDYS (n = 25)</th>
<th>With ExDYS (n = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV index [mL/m²]</td>
<td>169 (131–194)</td>
<td>155 (122–189)</td>
<td>172 (141–204)</td>
<td>0.2</td>
</tr>
<tr>
<td>LAV index [mL/m²]</td>
<td>66.7 ± 25.9</td>
<td>57.2 ± 19.6</td>
<td>76.7 ± 28.4</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>23.6 ± 6.0</td>
<td>25.6 ± 5.7</td>
<td>21.4 ± 5.7</td>
<td>0.01</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>17.1 ± 8.1*</td>
<td>14.4 ± 5.6</td>
<td>20 ± 9.5</td>
<td>0.02</td>
</tr>
<tr>
<td>MR [I–IV]</td>
<td>1 (1–2)</td>
<td>1 (0.75–2)</td>
<td>2 (1–3)</td>
<td>0.02</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.18 ± 0.38*</td>
<td>2.1 ± 0.46*</td>
<td>2.3 ± 0.23*</td>
<td>0.06</td>
</tr>
<tr>
<td>Max opposing wall delay [ms]</td>
<td>85.4 ± 41.2</td>
<td>74.2 ± 40*</td>
<td>97.5 ± 40*</td>
<td>0.04</td>
</tr>
<tr>
<td>rDYS</td>
<td>32 (66.6)</td>
<td>14 (56)</td>
<td>18 (78.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>At peak exercise:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max HR [bpm]</td>
<td>115.4 ± 22.1</td>
<td>116.1 ± 22.2</td>
<td>114.6 ± 22.5</td>
<td>0.81</td>
</tr>
<tr>
<td>Max workload [W]</td>
<td>80 (60–100)</td>
<td>80 (60–100)</td>
<td>60 (60–100)</td>
<td>0.37</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>24.4 ± 7.0</td>
<td>26.2 ± 6.6</td>
<td>22 ± 7.2</td>
<td>0.04</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>14.7 ± 6.2*</td>
<td>13.5 ± 6.2</td>
<td>16.1 ± 6</td>
<td>0.16</td>
</tr>
<tr>
<td>MR [I–IV]</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>2 (1–3)</td>
<td>0.007</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.07 ± 0.36*</td>
<td>1.9 ± 0.4*</td>
<td>2.1 ± 0.2*</td>
<td>0.11</td>
</tr>
<tr>
<td>CR</td>
<td>16 (33.3)</td>
<td>8 (32)</td>
<td>8 (34.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Max opposing wall delay [ms]</td>
<td>76.4 ± 42.8</td>
<td>40.6 ± 15.6*</td>
<td>115.2 ± 24.9*</td>
<td>&lt; 0.03</td>
</tr>
</tbody>
</table>

Data are shown as number (percentage), mean ± standard deviation, or median and interquartile range. #p-value < 0.05 for rest to peak exercise comparisons; CR — contractile reserve; E/e’ ratio — early diastolic mitral velocity to mean early diastolic velocity of the mitral annulus ratio; LAV index — left atrial volume normalised by body surface area; LVEDV index — left ventricular end-diastolic volume normalised by body surface area; LVEF — left ventricular ejection fraction; MR — mitral regurgitation; rDYS — dyssynchrony at rest; WMSI — wall motion score index.
DISCUSSION

In the present study we demonstrated that patients with ICM were more prone to have ExDYS as compared to patients with DCM. Patients with ExDYS had poorer systolic and diastolic LV function and more severe MR than patients without ExDYS. We also found that exercise caused changes in rDYS status in some patients. Exercise-induced resynchronisation was more likely to occur in patients with less advanced LV diastolic dysfunction, whereas exercise-induced dyssynchronisation occurred only in patients with ICM.

HFrEF remains one of the most important causes of mortality among cardiovascular diseases, being a real challenge for modern cardiology [6]. Improvement in our understanding of the pathophysiology of the failing heart is essential to bring improve the diagnosis and treatment of HFrEF.

Intraventricular dyssynchrony reflects inhomogeneous timing of contraction of different myocardial segments, caused by disturbed myocyte stimulation or impaired contractility [7, 8]. In the presence of dyssynchrony, systolic performance of the LV declines at an increased workload, promoting unfavourable cardiac remodelling [9].

Dyssynchrony has been associated with poorer exercise capacity, higher risk of HF decompensation, and death [10–12].

Cardiac resynchronisation therapy has become a standard therapeutic method directed at restoring coordinated ventricular contraction in patients with HFrEF. Despite its positive clinical impact, a significant portion of patients fail to respond sufficiently. Therefore, along with more precise lead positioning [13] and post-implantation device optimisation,
Ischaemic aetiology predicts exercise dyssynchrony in HFrEF patients

The main strength of our study is that it enriches a limited body of literature on the pathomechanisms of exercise-related LV dyssynchrony and helps to improve our understanding of

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this phenomenon. This was a prospective study which evaluated the role of rest and exercise LV dys synchrony assessed by echocardiography for LV systolic and diastolic functions, according to a predefined protocol.

Despite these advantages there are several limitations. It was a single-centre investigation with a relatively small number of participants. We used a limited number of LV dys synchrony parameters. We did not evaluate the role of exercise dys synchrony on the results of CRT. Despite these drawbacks, we believe that the consistency of the results validates the observations. Larger-scale prospective studies are needed to confirm our results.

In conclusion, ischaemic aetiology of HFrEF is an important predictor of ExDYS. Restoration of LV synchronicity during exercise is more likely in patients with less advanced LV diastolic dysfunction.

Conflict of interest: none declared

References


What is new? Our study provides a novel insight into the pathophysiology of exercise dyssynchrony in patients with heart failure with reduced ejection fraction. We showed that exercise dyssynchrony is closely related to ischemic aetiology of heart failure, as opposed to non-ischaemic one. We also showed that exercise caused changes in the rest dyssynchrony status in some patients. Exercise-induced resynchronisation was more likely in patients with less advanced left ventricular diastolic dysfunction, whereas exercise-induced dyssynchronisation occurred only in patients with ischaemic aetiology.