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

Authors: Jakub Stępniewski, Grzegorz Kopeć, Wojciech Magoń, Piotr Podolec

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

Brief title: Ischaemic predicts exercise dyssynchrony in HFREF patients

Jakub Stępniewski, Grzegorz Kopeć, Wojciech Magoń, Piotr Podolec
Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, John Paul II Hospital, Kraków, Poland

Address for correspondence:
Jakub Stępniewski, MD, Department of Cardiac and Vascular Diseases, Jagiellonian University Medical College, John Paul II Hospital in Kraków, Poland, ul. Prądnicka 80, 31-202 Kraków, Poland, tel: +48 12 614 22 87, mobile: +48 606 762 306, fax: +48 12 423 43 76, e-mail: jakub.stepniewski@gmail.com

WHAT’S NEW?
Our study provides a novel insight in the pathophysiology of exercise dyssynchrony in patients with heart failure with reduced ejection fraction. We showed that exercise dyssynchrony is closely related to ischaemic aetiology as opposed to non-ischaemic. We also showed, that exercise induced changes in the rest dyssynchrony status in some patients. Exercise - induced resynchronization was more likely in patients with less advanced LV diastolic dysfunction, whereas exercise - induced dyssynchronization occurred only in patients with ICM.

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

**Aims:** To investigate for predictors of ExDYS among patients with HFREF and prolonged QRS duration.

**Methods:** Consecutive patients with stable, chronic HF, LVEF<35%, sinus rhythm and QRS≥120ms were eligible. 2D echocardiography and tissue-Doppler were performed at rest and peak cyclo-ergometer exercise to assess LV systolic (LVEF) and diastolic function [mitral E-to-e’-wave velocities (E/e’)] and dyssynchrony. Dyssynchrony was defined as a maximal difference between time-to-peak systolic velocities of≥65ms from opposing basal segments.

**Results:** We included 48 patients (aged 63.7±12.2, 81.3% male). Ischaemic aetiology (ICM) was present in 23 (47.9%). Dyssynchrony at rest (rDYS) was present in 32 (66.6%) patients, while ExDYS in 23 (47.9%). ExDYS correlated with ICM, lower LVEF and higher E/e’ ratio. ICM remained significant predictor of ExDYS in multiple regression model (OR:4.3, 95%CI:1.2–15.7, p=0.03). On exercise, 19 (39.5%) patients changed the rDYS status. While, exercise-induced dyssynchronization was observed only in ICM patients, exercise-induced resynchronization 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 resynchronization 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 had also higher likelihood of cardiac resynchronization therapy (CRT) response [3]. Therefore, understanding mechanisms behind exercise-related dyssynchrony may improve patient selection for CRT.

In the present study, we aimed to investigate for 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. Patients were eligible for the study if they: (1) were in New York Heart Association (NYHA) functional class II–IV despite optimal medical therapy and optimal coronary revascularization; (2) had LV ejection fraction (LVEF) ≤ 35% and QRS duration ≥ 120 ms on 12-lead ECG; (3) were in sinus rhythm and had no exacerbations within past 3 months. Heart failure of ischaemic aetiology (ICM) was diagnosed if a patient had a history of myocardial infarction, coronary revascularization or a presence of angiographically significant stenotic lesions of >50% in coronary arteries, while non-ischaemic (DCM) when no history of coronary artery disease was present. Patients with a history of any cardiac implantable electronic devices, persistent atrial fibrillation, significant respiratory, neurological or orthopaedic disorder limiting 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 acquired by the authors themselves.

Echocardiography
All echocardiographic examinations were performed with the use of commercially available Vivid 7 device (GE Medical System, Horten, Norway) equipped with 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, 2-dimensional (2D) and Doppler parameters were calculated. Tissue Doppler imaging (TDI) data were recorded in apical 4-, 2- and 3-chamber views with sector size and depth optimization for the highest frame rate. Regional time-velocity curves (TVI) were produced offline from stored TDI colour images by placing sample volumes over 6 basal LV segments. All measurements were performed by an experienced echocardiographist by averaging 3 or more consecutive heart beats.
LV volumes and LVEF, as a measure of LV systolic function, were calculated with 2D-echocardiography from apical 4- and 2-chamber views, using the biplane disc summation method [4]. Similarly left atrial volume (LAV). Chambers volumes were normalized for body surface area (BSA).

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’).

Conventional 16–segment LV model was used to characterize regional contractility of the LV walls by scoring each segment from 1 - 4 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 visualized. Contractile reserve (CR) was defined as a decrease of WMSI by at least 0.20 from rest to peak exercise.

Severity of mitral regurgitation (MR) was evaluated qualitatively and graded from I – mild to IV – severe.

**Exercise stress echocardiography**

Following the rest examination, 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 Watts and raised every 2 minutes by 20 Watts. Tests were terminated on patients’ 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-minutes cycle. Each measurement was derived from at least 3 heart beats and expressed as mean. No changes to patients’ pharmacotherapy were made for the sole purpose of the stress test.

**Dyssynchrony evaluation**

Time-velocity curves of 6 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 6 basal segments. The differences between Ts of opposing wall segments were calculated to determine opposing wall delays. At least one opposing wall delay (maxTsD) greater or equal
to 65 milliseconds was indicative for rDYS and ExDYS. Ts were corrected for the RR interval using the Bazzet formula.

**Statistical analysis**

Categorical variables were described as counts and percentages and continuous variables as means ± standard deviations or median and interquartile range. We used the unpaired Student’s t-test for normally distributed variables, the Mann-Whitney U-test for non-normally distributed continuous data, and the chi-square 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’s t-test and Wilcoxon test.

We used univariate logistic regression analysis to assess 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 - nonspecific intraventricular conduction delay (IVCD), 1 - left bundle branch block (LBBB)], LV end-diastolic volume index (LVEDV index), markers of LV systolic (LVEF) and diastolic function (E/e’ ratio) and the presence of rDYS. Similarly, using univariate logistic regression models we investigated for association between exercise - induced changes of rDYS status including exercise - induced resynchronization and exercise - induced dyssynchronization 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), LV end-systolic volume index and markers of LV systolic (LVEF) and diastolic function (E/e’ ratio). 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<0.05. Statistical analyses were performed with Statistica PL software [StatSoft, Inc. (2014). STATISTICA (data analysis software system), version 12. www.statsoft.com] and MedCalc version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium).

**RESULTS**

**Patients characteristics**

There were 54 patients eligible for the study, of whom 6 were excluded due to insufficient quality of echocardiographic recordings. Among 48 enrolled patients aged 63.7 ± 12.2 years,
males represented the majority [39 (81.3%)]. ICM was present in 23 (47.9%) patients, while DCM in 25 (52.1%). Thirty (62.5%) patients were in NYHA class III, 12 (25%) in class II and 6 (12.5%) in class IV. Median N-terminal pro-B type natriuretic peptide level was 1667 [503 - 3309] pg/ml. Median QRS duration was 150 [120 – 160] ms with the LBBB morphology in 28 (58.3%) patients and nonspecific intraventricular conduction disturbances in 20 (41.7%). Patients were treated in accordance to contemporary guidelines [5]. Forty seven of them used beta blockers (97.9%) and angiotensin converting enzyme inhibitor or angiotensin receptor blocker; 44 (91.6%) used aldosterone receptor antagonist. Loop diuretics were used in 44 (91.6%) patients. Clinical characteristics of the study group is presented in Table 1.

**Rest and stress echocardiography**

Rest and stress echocardiographic examinations were completed successfully, with no significant adverse events. Stress examinations were terminated at mean workload of 76.2 ± 30.5 Watts. Detailed rest and exercise echocardiographic parameters are presented in Table 2. Left heart chambers were enlarged with median LVEDV\textsubscript{index} of 169 [131 – 194] ml/m\textsuperscript{2} and mean LAV\textsubscript{index} of 66.7 ± 25.9 ml/m\textsuperscript{2}. Global and regional LV systolic function was decreased with mean LVEF of 23.6 ± 6 % and mean WMSI 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 rest (2.07 ± 0.36, p<0.001) and became reduced by at least 0.20 at peak exercise in 16 (33.3%) patients, unveiling CR.

**Dyssynchrony**

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, whereas ExDYS in 23 (47.9%). Two-thirds [15 (65.2)] of patients with ExDYS had ICM as compared to patients without ExDYS, in whom 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 similarly 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 (OR: 4, 95% 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’ (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 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 (Figure 1 and 2). Fourteen (73.7%) regained LV synchronicity, whereas 5 (26.3%) became dyssynchronized. All 5 patients, who dyssynchronized at peak exercise had ICM. Among patients, who resynchronized at peak exercise, 11 (78.6%) had DCM and 3 (21.4%) ICM (p = 0.11). Exercise - induced resynchronization was associated with lower rest E/e’ ratio (OR: 0.85, 95% CI: 0.75 – 0.97, p = 0.02) and 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 resynchronization 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 dyssynchronization and its potential predictors.

**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 induced changes in rDYS status in some patients. Exercise - induced resynchronization was more likely in patients with less advanced LV diastolic dysfunction, whereas exercise - induced dyssynchronization occurred only in patients with ICM. HFREF remains one of the most important cause 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 improvement in the diagnosis and the treatment of HFREF.

Intraventricular dyssynchrony reflects inhomogeneous timing of contraction of different myocardial segments, caused by disturbed myocytes 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 [10,11,12].

Cardiac resynchronization 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 optimization, investigators have been seeking to refine selection criteria of the recipient population [14]. Presence of dyssynchrony has been suggested to improve identification of CRT responders. The weight of current evidence supports the use of echocardiography to detect LV dyssynchrony as a measure of CRT response [15-22].

Studies exploring pathophysiology of dyssynchrony has indicated, that it may be a dynamic phenomenon. In fact, dyssynchrony may persist or change during exercise, under pharmacological stress or by altering loading conditions. Lafitte et al., who studied the effects of exercise on LV dyssynchrony in a broad spectrum of HFREF patients showed, that ExDYS was present in up to 69% cases [23]. They also found, that up to 26% of patients may have either exercise induction or normalization of ventricular dyssynchrony. Lancellotti et al. demonstrated, that increase in LV dyssynchrony during exercise was strongly associated with the increase in severity of MR and impairment of LV stroke volume [1]. Similarly, dynamic impairment of intraventricular synchronicity during physical effort was strongly related to exercise incapacity, as demonstrated by D’Andrea et al. [2]. Furthermore, ExDYS has shown to be an important predictor of adverse outcome in patients with HFREF [24]. On the other hand however, presence of ExDYS has been found to be superior in predicting LV reverse remodelling and functional improvement after CRT than rDYS [3,25].

As majority of previous studies concentrated on the effects of exercise-induced changes of LV dyssynchrony on cardiac performance, prognosis or CRT response, we attempted to investigate the differences in clinical characteristics between patients with and without ExDYS among patients with HFREF and prolonged QRS duration, and to explore potential determinants of the presence of ExDYS.

We found in our study, that patients with ExDYS had poorer systolic and diastolic LV function and more severe MR than patients without ExDYS. There were no differences in QRS duration or prevalence of LBBB between the two groups. The prevalence of rDYS was similar. These findings may in part be attributed to the previously reported fact, that exercise-
induced dyssynchrony worsens LV systolic function and MR, irrespective of QRS duration or morphology [26]. Repeated dyssynchronization during exercise may augment impairment of cardiac performance with time. On the other hand, persistence of rDYS during exercise may reflect more advanced stage of the cardiac failure. Therefore, not only exercise-induced dyssynchronization as reported previously [27,28], but also persistence of rDYS on exercise may contribute to HF symptoms and reduced functional capacity and might have an impact on prognosis.

We also found, that the majority of patients with ExDYS had ICM, while those without ExDYS had DCM. Furthermore, all patients who lost synchronicity during exercise had ICM. Ischaemic aetiology was found to be an important determinant of ExDYS. Our data go beyond the findings of Lafitte et al., who showed that 80% of patients who experienced exercise-induced dyssynchronization had ICM [23]. We found, that patients with ICM are also more prone to remain dyssynchronized during exercise.

Presence of ExDYS and lack of its change during exercise in some of ICM and DCM patients, as shown in our study may suggest, that a part of myocardium has lost its ability to contract. On the contrary, dynamic restoration of LV synchronicity during exercise, observed mainly in patients with DCM, could reflect the presence of CR. These findings might suggest a close relationship between ExDYS and myocardial viability. There are however conflicting data regarding such relationship. Several studies have shown, that preserved CR helps to unmask LV dyssynchrony improving the process of CRT patients selection [29,30,31]. Some other have demonstrated the opposite. A study by AlJaroudi et al. has shown, that the presence of stress-inducible ischemia or the presence of scar on positron emission tomography perfusion images in patients with ICM favours the occurrence of ExDYS [32]. We observed in our study that, as LVEF and WMSI were more severely impaired in patients with ExDYS than in those without, exercise resulted in no change in LVEF and decrease in WMSI in both groups. The presence of CR was however not found to correlate with ExDYS or any change of LV dyssynchrony status either in ICM or DCM patients. This may suggest, that ExDYS is not solely dependent on the presence or absence of myocardial viability. Apart from systolic also diastolic properties of the LV may have an impact on the dyssynchrony status. We observed in our study, that more advanced diastolic dysfunction of the LV was associated with the presence of ExDYS especially in ICM patients. Furthermore, exercise-induced resynchronization was found to occur more likely in patients with lower rest and exercise E/e’ ratio. These findings are in line with data shown by Park et al., who demonstrated that modulation of LV loading conditions affects the dyssynchrony status [33].
They observed a significant decrease in the extent of LV dyssynchrony by reducing the LV filling pressure and its increase by elevating the afterload. Also, acute changes in the regional wall stress may alter electromechanical coupling within myocardial walls generating dynamic LV dyssynchrony. Increased myocardial stiffness may be a potential explanation why ICM patients are more prone to experience ExDYS.

ExDYS is an important element of HF pathophysiology. It has shown to be a promising parameter for selecting CRT candidates. Nonetheless, the mechanisms underlying ExDYS and its dynamic nature has not been entirely elucidated. Whether ExDYS indicates advanced stage of HF or potentially modifiable comorbidity requires further studies.

The main strength of our study is that it enriches limited body of literature on pathomechanisms of exercise - related LV dyssynchrony and helps to improve our understanding of this phenomenon. This was a prospective study, in which we evaluated the role of rest and exercise LV dyssynchrony assessed on echocardiography on LV systolic and diastolic function according to a predefined protocol. Despite these advantages there are several limitations. It was a single-centre investigation with a limited number of participants. We used limited number of LV dyssynchrony parameters. We did not evaluate the role of exercise dyssynchrony 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 validate 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


5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-1847. doi: 10.1093/eurheartj/ehs104.


Table 1. Clinical characteristics of the studied patients.

<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</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 [n (%)]</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/m²]</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 [n (%)]</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 [n (%)]</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>HR [beats per minute]</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>150 [120–160]</td>
<td>140 [120–160]</td>
<td>160 [122.5–160]</td>
<td>0.32</td>
</tr>
<tr>
<td>- 120–129 ms [n (%)]</td>
<td>13 (27)</td>
<td>8 (61)</td>
<td>5 (39)</td>
<td></td>
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<tr>
<td>- 130–149 ms [n (%)]</td>
<td>11 (23)</td>
<td>6 (55)</td>
<td>5 (45)</td>
<td></td>
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<tr>
<td>- ≥ 150 ms [n (%)]</td>
<td>24 (50)</td>
<td>11 (46)</td>
<td>13 (54)</td>
<td></td>
</tr>
<tr>
<td>LBBB/IVCD [n (%)]</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>Beta blocker [n (%)]</td>
<td>47 (97.9)</td>
<td>24 (96)</td>
<td>23 (100)</td>
<td>0.96</td>
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<tr>
<td>ACEi or ARB [n (%)]</td>
<td>47 (97.9)</td>
<td>24 (96)</td>
<td>23 (100)</td>
<td>0.96</td>
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<tr>
<td>ARA [n (%)]</td>
<td>44 (91.6)</td>
<td>22 (88)</td>
<td>22 (95.6)</td>
<td>0.66</td>
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<tr>
<td>Loop diuretics [n (%)]</td>
<td>44 (91.6)</td>
<td>23 (92)</td>
<td>21 (91.3)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

BMI — body mass index; NYHA — New York Heart Association; NT-proBNP — N-terminal pro-B-type natriuretic peptide; HR — heart rate; LBBB — left bundle branch block; IVCD — nonspecific intraventricular conduction disturbances; ACEi — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; ARA — aldosterone receptor antagonist

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>
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<th>p</th>
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</table>
At rest

| Variable                  | Univaria
table analysis | Multivaria
table logistic analysis (R² = 0.28) |
<table>
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<tr>
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<tbody>
<tr>
<td></td>
<td>OR [± 95%CI]</td>
<td>r</td>
</tr>
<tr>
<td>LVEDV_index [ml/m²]</td>
<td>169 [131–194]</td>
<td>155 [122–189]</td>
</tr>
<tr>
<td>LAV_index [ml/m²]</td>
<td>66.7 ± 25.9</td>
<td>57.2 ± 19.6</td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>23.6 ± 6.0</td>
<td>25.6 ± 5.7</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>17.1 ± 8.1#</td>
<td>14.4 ± 5.6</td>
</tr>
<tr>
<td>MR [I-IV]</td>
<td>1 [1–2]</td>
<td>1 [0.75–2]</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.18 ± 0.38#</td>
<td>2.1 ± 0.46#</td>
</tr>
<tr>
<td>Max opposing wall delay [ms]</td>
<td>85.4 ± 41.2</td>
<td>74.2 ± 40#</td>
</tr>
<tr>
<td>rDYS</td>
<td>32 (66.6)</td>
<td>14 (56)</td>
</tr>
</tbody>
</table>

At peak exercise

| Variable                  | Univaria
table analysis | Multivaria
table logistic analysis (R² = 0.28) |
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR [± 95%CI]</td>
<td>r</td>
</tr>
<tr>
<td>Max HR [beats per minute]</td>
<td>115.4 ± 22.1</td>
<td>116.1 ± 22.2</td>
</tr>
<tr>
<td>Max workload [watt]</td>
<td>80 [60–100]</td>
<td>80 [60–100]</td>
</tr>
<tr>
<td>sLVEF [%]</td>
<td>24.4 ± 7.0</td>
<td>26.2 ± 6.6</td>
</tr>
<tr>
<td>sE/e’ ratio</td>
<td>14.7 ± 6.2#</td>
<td>13.5 ± 6.2</td>
</tr>
<tr>
<td>sMR [I-IV]</td>
<td>1 [1–2]</td>
<td>1 [1–2]</td>
</tr>
<tr>
<td>sWMSI</td>
<td>2.07 ± 0.36#</td>
<td>1.9 ± 0.4#</td>
</tr>
<tr>
<td>CR [n (%)]</td>
<td>16 (33.3)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>sMax opposing wall delay [ms]</td>
<td>76.4 ± 42.8</td>
<td>40.6 ± 15.6#</td>
</tr>
</tbody>
</table>

LVEDV_index — left ventricular end-diastolic volume normalized by body surface area (BSA); LAV_index — left atrial volume normalized by BSA; LVEF — left ventricular ejection fraction; E/e’ ratio — early diastolic mitral velocity to mean early diastolic velocity of the mitral annulus ratio; MR — mitral regurgitation; WMSI — wall motion score index; rDYS — dyssynchrony at rest; CR — contractile reserve; # - p value <0.05 for rest to peak exercise comparisons

Table 3. Associations between the presence of exercise dyssynchrony and its predictors.
Table 4. Associations between exercise-induced LV resynchronization and its predictors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable logistic analysis (R² = 0.27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [± 95%CI]</td>
<td>r</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>0.85 [0.75 to 0.97]</td>
<td>-0.27</td>
</tr>
<tr>
<td>sE/e’ ratio</td>
<td>0.87 [0.75 to 0.99]</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

Abbreviations — see Table 2

**Figure 1.** Changes in the number of patients with ischaemic aetiology of heart failure with and without dyssynchrony at rest and at exercise

**Figure 2.** Changes in the number of patients with non-ischaemic aetiology of heart failure with and without dyssynchrony at rest and at exercise
Patients with ischemic etiology of heart failure

No Dyssynchrony

Rest

10

Exercise

5

3

Dyssynchrony

13

5

10
Patients with non-ischemic etiology of heart failure

<table>
<thead>
<tr>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Dyssynchrony</td>
<td>6</td>
</tr>
<tr>
<td>Dyssynchrony</td>
<td>19</td>
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</table>