Clinical research
Arrhythmia/electrophysiology

Early and late effects of cardiac resynchronization therapy on exercise-induced mitral regurgitation: relationship with left ventricular dyssynchrony, remodelling and cardiopulmonary performance

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Aims Exercise-induced mitral regurgitation (MR) bears a poor prognosis in patients with congestive heart failure (CHF). Cardiac resynchronization therapy (CRT) is associated with improved clinical outcome but its effects on exercise-induced MR remain undetermined. We investigated serial changes in functional MR in relation to left ventricular (LV) remodelling and cardiopulmonary performance after CRT.

Methods and results Twenty-eight patients with CHF (LV ejection fraction 25 ± 7%), broad QRS complex (171 ± 27 ms), and at least mild MR [effective regurgitant orifice (ERO) 0.25 ± 0.12 cm²] were studied with quantitative exercise echocardiography and cardiopulmonary exercise testing prior, within 1 week, and 3 months after CRT. Early after CRT, a decrease in L V dyssynchrony (from 54 ± 21 to 19 ± 7 ms, P = 0.001) and in MR at rest (ERO from 0.25 ± 0.12 to 0.20 ± 0.10 cm², P = 0.047) was observed. However, no change in exercise-induced increase in MR was observed (ERO from 0.34 ± 0.12 to 0.31 ± 0.16 cm², NS). Three months after CRT, a decrease in the mitral valve tenting area (from 3.3 ± 1.2 to 2.0 ± 0.6 cm², P < 0.001) and an increase in LV sphericity index (from 1.5 ± 0.3 to 1.8 ± 0.5, P < 0.001) were paralleled by an attenuation of exercise-induced MR (ERO 0.19 ± 0.06 cm², P = 0.001 vs. prior CRT). This was associated with an increase in LV ejection fraction (from 25 ± 7 to 35 ± 9%, P < 0.001), peak oxygen uptake (from 11.7 ± 2.4 to 13.7 ± 3.8 ml/kg/min, P = 0.001), and a decrease in NT-pro-BNP (from 2777 ± 1681 to 1963 ± 1361 pg/ml, P = 0.067).

Conclusion CRT is associated with acute decrease in resting MR but does not immediately attenuate exercise-induced MR. In contrast, only late, CRT-induced reversed LV remodelling and reduced mitral apparatus deformation are associated with a reduction in both resting and exercise-induced MR and with an improvement in cardiopulmonary performance.

KEYWORDS
Cardiac resynchronization; Heart failure; Exercise; Mitral insufficiency; Cardiopulmonary performance

Introduction
Chronic left ventricular (LV) dysfunction is frequently associated with functional mitral regurgitation (MR) caused by leaflets malcoaptation and negative chamber remodelling.1 Furthermore, in patients with congestive heart failure (CHF), the exercise-induced MR adversely affects cardiopulmonary performance2 and is associated with poor clinical prognosis.3 In patients with inducible MR, the poor prognosis appears to be related to the extent of exercise-induced MR rather than resting MR or severity of LV dysfunction.3 Cardiac resynchronization therapy (CRT) improves exercise tolerance, LV function,4,5 and survival in patients with CHF and cardiac dyssynchrony.6,7 Previous studies indicated that CRT is associated with acute improvement in resting MR.4–10 However, the effects of CRT on exercise-induced MR are not understood. In the present study, we postulated that CRT improves both resting and exercise-induced MR in parallel to LV remodelling and that the reduction in exercise-induced MR contributes to the better cardiopulmonary performance. Accordingly, we studied serial changes in MR and LV remodelling at rest and during exercise in parallel to cardiopulmonary performance early and late after CRT.
Methods

Patients

Among 37 consecutive patients undergoing CRT according to conventional criteria,11 28 were selected for the study based on the following inclusion criteria: presence of at least mild MR at rest, no echocardiographic evidence for organic mitral valve pathology, no previous history of mitral valve surgery, absence of aortic regurgitation >1 grade, and presence of sinus rhythm.

Biventricular pacemaker implantation

Biventricular pacing devices were implanted as previously described.12 The LV pacing electrode was positioned by transvenous approach through the coronary sinus into the lateral (eight patients) or posterolateral cardiac vein (20 patients). The device was programmed in DDD mode with a fixed short atrioventricular delay (115 ± 24 ms) to avoid pre-systolic MR. In nine patients, biventricular ICD devices were implanted because of episodes of sustained ventricular tachycardia and/or inducible ventricular arrhythmias.

Cardiopulmonary exercise testing

The oxygen uptake (VO2), VCO2, and VE were continuously measured with a computerized breath-by-breath analyzer. Peak VO2 was defined as the highest value recorded during the last 30 s of exercise. Ventilatory anaerobic threshold was calculated using the V-slope method.

The peak VO2 was expressed in mL/kg/min. Exercise tests were always performed at the same period of the day. All patients performed a maximal exercise test as evidenced by a respiratory exchange ratio at peak exercise >1.10. An increase in peak VO2 > 1.1 mL/kg/min was considered as clinically meaningful improvement.3

Brain natriuretic peptide measurement

Venous levels of Nt-pro-BNP (Elecys 2010 -Roche diagnostics, GmbH, 68298 Mannheim, Germany) were determined from blood samples collected prior and after CRT.20

Statistics

On the basis of the data of Lancellotti et al.,7 we expected a change in exercise ERO from baseline to 3 months follow-up of 0.18 cm² with a standard deviation of 0.14 cm². Using a power of 0.80, we calculated a sample size of 17 for a significance level of 0.05 and a sample size of 26 for a significance level of 0.025 (for the Bonferroni adjustment for multiple comparisons). All data are presented as mean ± SD. Gaussian distribution of data was tested by means of the Kolmogorov-Smirnov test. A two-sided non-paired, paired t-test and Fisher's exact test were used as appropriate. In the case of non-normality, the Wilcoxon paired test or the Mann-Whitney U test (for non-paired observations) was used. Bonferroni's method for multiple comparisons was used where needed. A repeated measures ANOVA followed by Bonferroni correction was used for comparison of respective conditions early and late CRT effects when compared with baseline. The Huynh–Feldt correction was used if the sphericity assumption was not met. Post hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons. The Pearson or Spearman correlation coefficients were used to measure the linear association between various parameters as appropriate.

Results

Out of 28 patients enrolled in the study, one patient died 2 days after CRT due to progression of heart failure. One patient was unable to exercise within 1 week after CRT due to worsening of heart failure. In one patient, the pacemaker was removed because of infection complication after 2 months. Three months after CRT, one additional patient was not able to exercise due to a hip fracture.

Baseline characteristics

Baseline demographic and clinical characteristics are given in Table 1. In all patients, medical treatment with beta-blockers or ACE/AT1-inhibitors remained unchanged between baseline and 3 months follow-up. Baseline echocardiography characteristics prior to CRT are given in Table 2. As shown in Figure 1, in the entire study population, exercise was associated with variable changes in LV dyssynchrony and the extent of LV dyssynchrony did not change when compared with rest. On the other hand, exercise testing was associated with an increase in ERO in all but five patients, and overall, ERO and regurgitant volume of MR increased was assessed only from the time intervals measured in basal LV septal, posterolateral, and right ventricular segments.

Exercise protocol

Patients underwent symptom-limited exercise test in semi-supine position with initial workload of 25 W for 2 min and with 10 W load increments each minute. Blood pressure was measured at rest, at the end of the each load increment, and at peak exercise. Doppler echocardiography recordings were taken during peak exercise and within 1 min after its termination. At peak exercise, LV morphology and recordings of MR were obtained in all patients. Tissue doppler imaging (TDI) recordings of time interval for assessment of LV dyssynchrony in basal segments were successfully obtained in all but five patients. In these patients, LV dyssynchrony

Doppler echocardiography

Two-dimensional Doppler echocardiography was performed with a commercially available system (Accuson, Sequoia C512, USA) at baseline, within 1 week and at 3 months after CRT. Images were acquired in semi-supine position at rest and at peak exercise. Following morphological and functional analyses were performed from digitally and video-stored images off-line. First, LV end-diastolic and end-systolic volumes and LV ejection fraction were calculated using the biplane Simpson's formula.13 LV systolic sphericity index, defined as the ratio of length to width of the LV at end-systole was used as an index of LV remodelling.14,15 Second, mitral valve deformation was assessed from changes in tenting area and mitral annulus diameter. Tenting area was defined as the area between the annulus and the mitral valve leaflets from the parasternal long-axis view at mid-systole.16 Mitral annular diameter was measured in apical four-chamber view at end-diastole. Third, the degree of MR was assessed using proximal isovelocity surface area method and quantitative Doppler method and quantified as effective regurgitant orifice (ERO) and regurgitant volume.17,18 The results of these two methods were averaged and used for further analyses. In addition, pulsed-wave tissue Doppler imaging was used to assess LV dyssynchrony in interventricular dyssynchrony from regional time intervals between the onset of QRS complex and the onset of systolic myocardial velocity in basal segments of the left and right ventricles.19 LV dyssynchrony was defined as the maximum delay between basal LV segments. Interventricular dyssynchrony was determined as the difference between the most delayed basal segment of the LV and free right ventricular wall delay. Finally, the myocardial systolic velocity (Sm) from the lateral annulus was acquired. LV contractile reserve was assessed as the difference between resting and exercise-induced increase in Sm (ΔSm).

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when compared with rest. Note, a significant relationship was observed between the exercise-induced LV dyssynchrony and exercise-induced ERO (Figure 1). In addition, exercise was associated with an increase in tenting area, but no significant changes in mitral annulus diameter or sphericity index. Finally, an increase in Sm and global LV ejection fraction was noted when compared with rest. No new, exercise-induced regional wall motion abnormalities were observed.

Discussion
The present study investigated the effects of CRT on resting and exercise-induced MR early and late after resynchronization. The main findings can be summarized as follows: (i) a reduction in LV dyssynchrony by CRT is associated with improved cardiopulmonary performance. In contrast, exercise-induced MR is significantly attenuated later in parallel to reversed mitral and LV remodelling; (iii) reduction in exercise-induced MR appears to be associated with improved cardiopulmonary performance.

Left ventricular dyssynchrony and exercise-induced mitral regurgitation
Functional MR is a critical factor in symptomatology of patients with CHF.\textsuperscript{16} The extent of exercise-induced MR adversely affects cardiopulmonary performance\textsuperscript{2} and is associated with poor clinical outcome.\textsuperscript{3} Earlier studies indicated that rest and exercise-induced MR are related to mitral deformation given by greater mitral tenting area and coaptation height resulting in increased transmitial pressure gradient.\textsuperscript{21,22} In addition, more recent studies demonstrated that changes in MR from rest to exercise are closely related to the extent of LV dyssynchrony at rest\textsuperscript{23,24} supporting the role of functional MR in QRS widening and progression of heart failure in patients with LV dyssynchrony.\textsuperscript{25} Our observation of a close relationship between the LV dyssynchrony and MR at peak exercise is

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 28</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
</tr>
<tr>
<td>Male/Female</td>
<td>23/5</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Ischemic/Idiopathic</td>
<td>14/14</td>
</tr>
<tr>
<td>CABG</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>Inducible VT/VF</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>ICD Implantation</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>Prior RV pacing</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>ACE-I/ATR I blockers</td>
<td>28 (100%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>Spironolacton</td>
<td>23 (82%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10 (36%)</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme-inhibitors; ATR, angiotension receptor; CABG, coronary artery bypass grafting; CAD, coronary artery disease; ICD, implantable cardioverter-defibrillator; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.
consistent with these findings and supports the role of LV
dysynchrony in the pathophysiology of exercise-induced MR.

Exercise-induced mitral regurgitation and
cardiopulmonary performance after cardiac resynchronization therapy

In patients with CHF and dyssynchrony, CRT improves LV
function, exercise tolerance,4,5 and survival.6,7 Although
the majority of studies suggested cardiac resynchronization
with subsequent LV remodelling14,15,19,26–28 as major under-
lying mechanism, a number of studies indicate that acute
improvement in resting MR could also mediate beneficial
effects of CRT upon LV remodelling.4–9 However, it remains
unknown whether and how CRT attenuates exercise-induced
MR. The present exercise echocardiography study provides
several novel insights into the serial changes of MR and
mechanisms underlying benefit of CRT (Figure 4). First, improvement in MR at rest occurred immediately after CRT and was related to the extent of exercise-induced LV dyssynchrony and contractile reserve prior to implantation. This is consistent with previous studies indicating acute improvement in MR as a result of reduced dyssynchrony and increased closing force of the mitral valve.8–10 These data suggest improved synchronization and acute recruitment of contractility as underlying mechanisms of immediate attenuation of functional MR by CRT. Nevertheless, in our study, CRT failed to attenuate immediately exercise-induced MR. Likewise, CRT induced only a moderate effect on exercise-induced LV dyssynchrony. In fact, the extent of exercise-induced LV dyssynchrony remained proportional to the extent of exercise-induced MR. On the other hand, 3 months later, CRT led to a significant reversed remodelling and entirely abolished exercise-induced LV dyssynchrony. This was paralleled by a decrease in the tenting area leading to a further reduction in MR at rest as well as to a significant attenuation of exercise-induced MR. Hence, attenuation of exercise-induced MR by CRT is gradual and related to several synergistic mechanisms. Early reduction of LV dyssynchrony and recruitment of contractile reserve are primary effects. They trigger reversed LV remodelling which together with mitral deformation further improves resting MR and attenuates exercise-induced functional MR. Reduction in exercise-induced MR in parallel to reversed LV remodelling translates into improved LV function and cardiopulmonary performance. It is of note that patients with improved cardiopulmonary performance had lower extent

![Figure 2](image-url) Serial changes in left ventricular dyssynchrony and mitral regurgitation at rest and at peak exercise: before cardiac resynchronization therapy, early after cardiac resynchronization therapy, and late (3 months) after cardiac resynchronization therapy. Abbreviations as in Figure 1.

![Figure 3](image-url) Example of changes in rest and exercise induced mitral regurgitation at baseline, early, and later after cardiac resynchronization therapy. Upper panel shows the resting conditions with colour-flow mapping of the mitral regurgitation, lower panel shows the changes in the mitral regurgitation at peak exercise. Early after cardiac resynchronization therapy, the extent of exercise-induced mitral regurgitation was comparable to baseline, despite a reduction in the resting mitral regurgitation. Significant attenuation of exercise-induced mitral regurgitation was noted only later after cardiac resynchronization therapy. Note that attenuation of exercise-induced mitral regurgitation was paralleled by reduction in left ventricular dimensions.
of exercise-induced MR when compared with patients with no or minimal increase cardiopulmonary performances. Though this may be related to differences in effects of CRT on mitral deformation between both subgroups, identification of factors responsible for greater reduction of exercise-induced MR in patients with improved peak VO₂ requires further studies. Nevertheless, mechanistic observations into serial changes in exercise-induced MR support the hypothesis that its reduction may underlie improved cardiopulmonary performance and improved survival after CRT.

**Limitations**

In patients with ischaemic cardiomyopathy, exercise-induced ischaemia could have been responsible for exercise-induced MR. However, similar to the study of Lancellotti et al.,²⁹ none of our patients developed

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**Table 3** Early and late effects of cardiac resynchronization therapy on cardiopulmonary performance

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Early CRT</th>
<th>Late CRT</th>
<th>Main effect</th>
<th>P-values for post hoc comparisons</th>
<th>P-values for post hoc comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early vs. baseline</td>
<td>Late vs. baseline</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>P-value</td>
<td>η²</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Workload (W)</td>
<td>69 ± 18</td>
<td>67 ± 24</td>
<td>78 ± 25</td>
<td>$F(2,30) = 4.4$</td>
<td>0.021</td>
<td>0.23</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>5.9 ± 1.7</td>
<td>6.2 ± 2.2</td>
<td>6.9 ± 2.6</td>
<td>$F(2,28) = 3.1$</td>
<td>0.061</td>
<td>0.18</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>11.7 ± 2.4</td>
<td>12 ± 3.4</td>
<td>13.7 ± 3.8</td>
<td>$F(2,20) = 11.4$</td>
<td>0.001</td>
<td>0.53</td>
</tr>
<tr>
<td>Nt-pro-BNP (pg/mL)</td>
<td>2777 ± 1681</td>
<td>2871 ± 1978</td>
<td>1963 ± 1361</td>
<td>$F(1.3,18.8) = 4.4^b$</td>
<td>0.041</td>
<td>0.23^b</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0 ± 0.6</td>
<td>2.9 ± 0.6</td>
<td>1.9 ± 0.3</td>
<td>$F(2,40) = 39.3$</td>
<td>&lt;0.001</td>
<td>0.66</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>171 ± 27</td>
<td>143 ± 26</td>
<td>143 ± 26</td>
<td>$F(1,20) = 14.5^b$</td>
<td>0.001</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*P*-value of <0.05 considered to be statistically significant.

*With Bonferroni’s corrections.

*Sphericity assumption not met.

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**Figure 4** Cardiac resynchronization and proposed mechanisms contributing to early and late effects of cardiac resynchronization therapy on mitral regurgitation at rest and during exercise. For details, see Discussion. Abbreviations as in Figure 1.
exercise-induced angina or new wall motion abnormalities. Likewise, there were no differences in the extent of exercise-induced MR between patients with ischaemic and idiopathic cardiomyopathy. Nevertheless, this is a mechanistic study and the postulate that CRT improves prognosis by attenuation of exercise-induced MR requires future prospective studies. Several limitations related to pulsed-tissue Doppler-derived assessment, such as angle-dependency or sole analysis of basal segments, should be also acknowledged and novel methods such as speckle tracking or three-dimensional-derived assessment could be used as an alternative to track more reliably changes in LV dysynchrony during the exercise. To minimize pitfalls of the MR quantification by using single method, MR was quantified using two methods as previously recommended.\(^1,8,9,17\) Furthermore, changes in ERO were paralleled by similar changes in mitral regurgitant volume and regurgitant fraction. While inherent limitations of Doppler assessment of LV dyssynchrony or MR may be an issue for the comparative studies, their choice should not invalidate the principle findings of the current study as to mechanism underlying improvements in MR and cardiopulmonary performance.

**Clinical implications**

CRT is associated with acute improvement in MR, but it does not attenuate exercise-induced increase in MR early after CRT. In contrast, after 3 months, CRT results in the LV and mitral reversed remodelling in parallel to a reduction in both exercise-induced LV dyssynchrony and exercise-induced MR. Reduction in exercise-induced MR could represent the main mechanism contributing to the beneficial effects of CRT on survival of patients with CHF.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Conflict of interest:** none declared.

**References**


