Exercise stress echocardiography is superior to rest echocardiography in predicting left ventricular reverse remodelling and functional improvement after cardiac resynchronization therapy

Guido Rocchi*, Matteo Bertini, Mauro Biffi, Matteo Ziacchi, Elena Biagini, Ilaria Gallelli, Cristian Martignani, Elena Cervi, Marinella Ferlito, Claudio Rapezzi, Angelo Branzi, and Giuseppe Boriani

Institute of Cardiology, University of Bologna, Azienda Ospedaliera S. Orsola-Malpighi, via Massarenti 9, 40138 Bologna, Italy

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Aims
Cardiac resynchronization therapy (CRT) improves functional capacity and survival in heart failure. However, one-third of patients fail to respond to CRT. Resting left ventricular (LV) dyssynchrony assessed by echocardiography (ECHO) showed discordant results in identifying CRT responders. LV dyssynchrony can totally change during exercise. Aim of this study was to evaluate whether exercise dyssynchrony could select responders to CRT.

Methods and results
Sixty-four patients scheduled for CRT implantation performed bicycle exercise ECHO in semi-supine position on an exercise tilting table before and 6 months after CRT implantation. Tissue Doppler imaging (TDI) was acquired both at rest and during exercise to detect LV mechanical dyssynchrony. Predictive values for CRT response were 70% for rest TDI and 89% for exercise TDI ($P = 0.01$). Exercise LV dyssynchrony was the only parameter independently associated with follow-up improvement of rest ejection fraction and LV volume during multivariable analysis ($P < 0.001$). Functional improvement at 6-min walking test was statistically higher in patients with exercise dyssynchrony ($P = 0.005$), and not different considering rest dyssynchrony ($P = 0.30$).

Conclusion
Exercise intraventricular dyssynchrony assessed by exercise TDI ECHO is a strong independent predictor of CRT response. It could be used to select candidates for CRT, thus reducing ineffective implantations of biventricular pacemakers.

Keywords
Exercise echocardiography • Tissue Doppler imaging • Cardiac resynchronization therapy • Heart failure

Introduction
Cardiac resynchronization therapy (CRT) improves functional capacity and survival in patients with drug-refractory heart failure (HF).$^{1-3}$ However, one-third of patients fail to respond to CRT, thus underlining the need for better selection criteria.$^{1,2,4-6}$ Observational studies using echocardiography (ECHO) at rest have demonstrated that the mechanism leading to clinical improvement is the resynchronization of pre-existing left ventricular (LV) dyssynchrony.$^{7-10}$ Tissue Doppler imaging (TDI) has been shown to be a promising ECHO method for identifying LV dyssynchrony.$^{7-10}$ Dyssynchrony, assessed by TDI regardless of QRS duration, has therefore been proposed as a selection criterion for CRT.$^{11}$ However, the first multicenter study (PROSPECT) recently reported disappointing results: no ECHO measure of mechanical dyssynchrony at rest was really useful in identifying patients likely...
to respond to CRT.\textsuperscript{12,13} In the recently published RethinQ study, echo parameters assessed at rest also failed to predict functional response to CRT in patients with narrow QRS.\textsuperscript{14} All ECHO measurements in the PROSPECT and RethinQ studies were carried out at rest; indeed, a recent study reported that exercise may totally change the presence and the extent of LV dysynchrony by modification of cardiac output and mitral regurgitation (MR).\textsuperscript{15} Few data on the role of LV exercise dysynchrony during exercise are yet available,\textsuperscript{15,16} and no experience regarding the predictive value of TDI exercise ECHO in selecting patients for CRT has been reported. We therefore conducted an exercise ECHO study to understand whether LV exercise dysynchrony can be used as a selection criterion for CRT. Exercise ECHO was also repeated after 6 months to understand whether poor exercise resynchronization could cause lack of response to CRT.

\section*{Methods}

\subsection*{Patients}

Seventy-five patients were initially screened for enrolment in the study. Exclusion criteria were primary severe MR (two patients), atrial fibrillation (five patients) and rest dyspnoea at the time of the stress test (one patient). Thus, 67 consecutive patients with HF NYHA III–IV scheduled for implantation of a CRT device were enrolled for the exercise stress ECHO starting since January 2006 until September 2007. A formal sample size calculation was not performed \textit{a priori}. It was decided to analyse the results after the enrolment of at least 60 patients, which was comparable with the number of patients enrolled in previous studies evaluating the predictive value of rest LV dyssynchrony.\textsuperscript{6–10} Indications for CRT implantation were sinus rhythm, LV systolic dysfunction with an ejection fraction (EF) ≤ 35\%, and QRS duration >120 ms as suggested by current guidelines. The NYHA class considered was the maximum functional class reached, but at the time of inclusion all patients had stable optimized medical therapy, which was not changed during follow-up, and were able to undergo at least minimal exercise. No patient had a history of acute coronary syndrome or revascularization in the previous 6 months. Three of the 67 patients were not able to perform a semi-supine exercise test and were excluded from the study (two patients affected by Becker muscular dystrophy with peripheral muscle disease, and one patient because of severe obesity); thus, 64 patients were finally enrolled in the study. Coronary angiography was performed in all patients to determine the aetiology of the dilated cardiomyopathy (DCM). All patients provided written informed consent.

\subsection*{Study protocol}

Rest and exercise ECHO were performed before CRT implantation and at 6-month follow-up. Response to CRT was defined as a reduction of end-systolic LV volume ≥ 15\% compared with baseline and an improvement of EF > 5\% (absolute value) at 6-month follow-up, both assessed at rest ECHO. These endpoints, indicating LV reverse remodelling, have already been used in several studies to differentiate responders to CRT from non-responders, and have been shown to be independent predictors of prognosis.\textsuperscript{6,12,17} In addition, a 6-min walking test was performed before and 6 months after CRT.

\subsection*{Biventricular device implantation}

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Contak-Renewal 4, Boston-Guidant, St. Paul, MN, USA; Insyne III, Marquis, Medtronic, Minneapolis, MN, USA; Epic HF, St. Jude Medical, Sylmar, CA, USA). All devices were implanted by transvenous approach. The LV pacing lead was placed in a lateral (23 patients) or postero-lateral (41 patients) cardiac vein.

\subsection*{Biventricular pacemaker optimization}

Before discharge from hospital, an ECHO optimization of the pacing intervals was performed in all the patients. Atioventricular delay was optimized to achieve the longest diastolic time according to the longest mitral inflow filling time detected by pulsed Doppler. At the optimal atioventricular delay, interventricular (VV) optimization was performed according to the greatest LV stroke volume based on the velocity-time integral assessed by pulsed Doppler positioned at LV outflow tract. Seven different pacemaker settings were tested: simultaneous right ventricle (RV) and LV output, LV pre-excitation (20, 40, and 60 ms), RV pre-excitation (20 and 40 ms), and LV stimulation alone.\textsuperscript{18,19}

\subsection*{Exercise echocardiography}

A symptom-limited bicycle exercise stress test was performed in semi-supine position on an exercise echo-titling table (stress echo supine ergometer, Ergoselect 1200 EL, Ergoline GmbH, Bitz, Germany). The workload was increased 25 W every 2 min. Blood pressure and 12-lead ECG were recorded every minute. ECHO images were assessed at baseline and at peak exercise using a Philips Sonos 5500 Ultrasound System (Philips Ultrasound, Andover, MA, USA) equipped with a harmonic fusion imaging probe (s3) and off-line cineloop analysis software. All images were recorded digitally and analysed off-line and each parameter was measured on an average of three consecutive beats both at rest and during exercise. LV volumes and EF were calculated using the biplane modified Simpson’s method. HR was quantified by the colour-area method.

\subsection*{Tissue Doppler imaging and LV dyssynchrony evaluation}

Pulsed tissue Doppler imaging was acquired using two-, three-, and four-chamber apical views to assess the longitudinal movement of the LV. To determine LV dyssynchrony, the sample volume was placed in the basal portion of the posterior and anterior septum, lateral, inferior, anterior, and posterior walls; peak systolic velocities were obtained. The time-to-peak systolic velocities were measured for the six LV basal segments. Each segmental electromechanical delay was defined as the time from the onset of the QRS to the peak of the systolic (S) TDI wave (Figure 1). LV dyssynchrony parameters were normalized for the RR interval [(dyssynchrony delay/RR interval) × 1,000] to compare resting and exercise values, as previously described.\textsuperscript{15} Two different TDI methods were used for LV dyssynchrony evaluation: (i) Maximum difference of electromechanical delay among four LV basal segments (cut-off ≥ 65 ms) published by Bleeker et al.\textsuperscript{11} that was used as the reference method. (ii) The standard deviation (SD) of the electromechanical delays of the six LV basal segments (cut-off: SD ≥ 32 ms), similar to the method published by Yu et al.,\textsuperscript{6} that was assessed for comparison with the former method. QRS duration was also assessed from the surface electrocardiogram as a marker of LV dyssynchrony.

\subsection*{Viability assessment of the postero-lateral wall}

In all patients with ischaemic DCM, the presence of contractile reserve of the postero-lateral wall was assessed during exercise ECHO to differentiate transmural from non-transmural scar; because a previous
study based on magnetic resonance imaging (MRI) showed that patients with postero-lateral transmural scar do not respond to CRT. Using a 17-segment LV model and a four-point wall motion scale, a comparison of rest and exercise ECHO was performed by two blinded observers in an off-line analysis to assess the contractile reserve of four segments (the basal and the mid segments of posterior and lateral walls). To avoid the lack of wall thickening at peak exercise owing to ischaemia, the analysis was performed at each workload step starting from 25 W. Viability of the postero-lateral wall was defined as a contractile reserve \( \geq 1/4 \) segments at any exercise step.

**Statistical analysis**

Continuous data are presented as mean ± SD; dichotomous data are presented as numbers and percentages. Data within patient-groups (responders vs. non-responders) were compared using unpaired Student's t-test (continuous variables) and Wilcoxon tests. Pearson's correlation was used to determine the relations between LV dyssynchrony (rest and stress) and changes in 6 min walking test, LV end-systolic volume, and LVEF. Multivariable logistic regression analysis was performed on all variables listed in Table 3, to identify any possible variables related to a positive response to CRT. Model discrimination was assessed using c-statistic and model calibration was assessed using Hosmer–Lemeshow statistic. To assess linearity, we categorized continuous variables as intervals and performed the score test for trend of odds on the proportion of responders at each interval. Sensitivity, specificity, positive, negative, and overall predictive values were calculated both for rest and exercise ECHO dyssynchrony and were compared using a Z-test. All statistical tests were two-sided, and a \( P \)-value \( < 0.05 \) was considered significant. The software program SPSS 14.0 and STATA 9.0 were used for statistical analysis.

**Variability analysis**

Intraobserver variability was assessed in two different blind evaluations 30 days apart, whereas interobserver variability was assessed by two different observers (G.R. and M.B.). Intraobserver and interobserver agreement for LV dyssynchrony using the cut-off \( \geq 65 \) ms among four LV basal segments was calculated at rest and at peak exercise: intraobserver agreement was 98.1% \( (k = 0.96, SE = 0.131) \) both at rest and at peak exercise, whereas interobserver agreement was 94.4% both at rest and at peak exercise \( (k = 0.89, SE = 0.122) \). The intra and interobserver variability of the study endpoints (rest LVEF and rest LV end-systolic volumes) were also assessed in a subgroup of 20 patients using Bland and Altman analysis and are expressed as mean difference of the two readings with 95% confidence interval (CI) and the limits of agreements with their 95% CI. Accordingly, EF intraobserver variability mean difference was 0.2 (95% CI = 0.4 to

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**Figure 1** A tissue Doppler imaging during exercise echocardiography before biventricular pacemaker implantation in a patient with intraventricular dyssynchrony by both methods [maximal difference of electromechanical delay = 95 ms (cut-off \( \geq 65 \) ms)] and standard deviation of the electromechanical delays of the six LV basal segments of 37 ms (cut-off: SD \( \geq 32 \) ms).
0.8) and 95% limits of agreement were $-2.3$ (95% CI: $-3.4$ to $-1.3$) to $2.7$ (95% CI: $1.6$–$3.7$); EF interobserver variability mean difference was $0.8$ (95% CI: $0.1$–$1.5$) and 95% limits of agreement were $-2.3$ (95% CI: $-3.6$ to $-1.0$) to $3.9$ (95% CI: $2.6$–$5.2$); LV end-systolic volumes intraobserver variability mean difference was $1.5$% (95% CI: $0.0$–$3.0$) and 95% limits of agreement were $-2.1$% to $7.7$% (95% CI: $5.1$–$10.3$); LV end-systolic volumes interobserver variability mean difference was $2.8$% (95% CI: $0.8$–$4.9$%) and 95% limits of agreement were $-5.8$% (95% CI: $-9.4$ to $-2.2$%) to $11.5$% (95% CI: $7.9$–$15.1$%).

**Results**

Sixty-four patients were enrolled in the study. Mean age was 64 ± 11 years, 25% females (16/64), 30% of patients (19/64) had ischaemic DCM, whereas 70% (45/64) had idiopathic DCM. Technically adequate ECHO recordings were obtained both at rest and during exercise in all patients. Mean exercise duration was 5.0 ± 1.8 min and mean peak workload was 68 ± 24 W. A follow-up was obtained in all patients at 6.2 ± 0.8 months. At follow-up, 67% (43/64) of patients had LV reverse remodelling (responder patients), whereas 33% (21/64) of patients were non-responders. The 6-min walking test improvement was significantly different between responders and non-responders ($\Delta = +105 \pm 101$ vs. $+21 \pm 76$ m; $P = 0.001$). Responders and non-responders baseline characteristics were similar (Table 1).

Intraventricular dysynchrony, both at rest and during exercise, was significantly greater in responder than in non-responder patients (rest dysynchrony: $91 \pm 30$ vs. $60 \pm 41$ ms, $P = 0.001$; LV exercise dysynchrony $133 \pm 41$ vs. $41 \pm 43$ ms, $P < 0.0001$).

**Predictors of improvement after cardiac resynchronization therapy**

**QRS duration**

QRS duration was not predictive of CRT response and was similar in responder and non-responder patients both at rest (162 ± 26 vs. 155 ± 24 ms; $P = 0.34$) and during exercise (149 ± 25 vs. 148 ± 38 ms; $P = 0.86$).

**Rest and exercise tissue Doppler**

Both TDI methods for the assessment of intraventricular dysynchrony: (1) maximal difference of electromechanical delay among four LV basal segments, cut-off ≥ 65 ms; (2) SD of the electromechanical delays of the six LV basal segments, cut-off: SD ≥ 32 ms obtained consistent results either at rest (97%, 62/64 patients) and at peak exercise (98%, 63/64 patients). Using the maximal difference of electromechanical delay among four LV basal segments, cut-off ≥ 65 ms, as reference method to assess LV dysynchrony, both EF improvement and LV volume reduction after CRT were greater in patients with exercise LV dysynchrony compared to stable EF and LV volumes.

<p>| Table 1 Baseline characteristics of responders vs. non-responders to CRT |
|----------------------------------|-------------------|------------------|------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 43)</th>
<th>Non-responders (n = 21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 10</td>
<td>61 ± 13</td>
<td>0.094</td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>30 (70)</td>
<td>18 (86)</td>
<td>0.140</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic, n (%)</td>
<td>9 (24)</td>
<td>11 (53)</td>
<td>0.042</td>
</tr>
<tr>
<td>Non-ischaemic, n (%)</td>
<td>34 (76)</td>
<td>10 (47)</td>
<td></td>
</tr>
<tr>
<td>Maximum NYHA class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>41 (95)</td>
<td>20 (95)</td>
<td>0.541</td>
</tr>
<tr>
<td>LV</td>
<td>2 (5)</td>
<td>1 (5)</td>
<td>0.882</td>
</tr>
<tr>
<td>6-min walking test (m)</td>
<td>336 ± 124</td>
<td>393 ± 87</td>
<td>0.063</td>
</tr>
<tr>
<td>Exercise minutes</td>
<td>5 ± 1.9</td>
<td>5 ± 1.8</td>
<td>0.380</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>89</td>
<td>89</td>
<td>0.670</td>
</tr>
<tr>
<td>QRS wide (ms)</td>
<td>162 ± 26</td>
<td>155 ± 24</td>
<td>0.350</td>
</tr>
<tr>
<td>Rest LVEF (%)</td>
<td>24 ± 5</td>
<td>25 ± 5</td>
<td>0.382</td>
</tr>
<tr>
<td>Rest LV end-diastolic volume (mL)</td>
<td>227 ± 76</td>
<td>236 ± 56</td>
<td>0.658</td>
</tr>
<tr>
<td>Rest LV end-systolic volume (mL)</td>
<td>175 ± 66</td>
<td>177 ± 47</td>
<td>0.882</td>
</tr>
<tr>
<td>Rest severe mitral regurgitation, n (%)</td>
<td>15 (35)</td>
<td>8 (38)</td>
<td>0.507</td>
</tr>
<tr>
<td>Exercise LVEF (%)</td>
<td>30 ± 7</td>
<td>28 ± 7</td>
<td>0.521</td>
</tr>
<tr>
<td>Exercise LV end-diastolic volume (mL)</td>
<td>220 ± 62</td>
<td>232 ± 59</td>
<td>0.483</td>
</tr>
<tr>
<td>Exercise LV end-systolic volume (mL)</td>
<td>158 ± 54</td>
<td>168 ± 51</td>
<td>0.519</td>
</tr>
<tr>
<td>Exercise severe mitral regurgitation, n (%)</td>
<td>26 (60)</td>
<td>13 (62)</td>
<td>0.567</td>
</tr>
<tr>
<td>LV rest dysynchrony (ms/RR)</td>
<td>91 ± 30</td>
<td>60 ± 41</td>
<td>0.001</td>
</tr>
<tr>
<td>LV exercise dysynchrony (ms/RR)</td>
<td>133 ± 41</td>
<td>51 ± 43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CRT, cardiac resynchronization therapy; LV, left ventricle; NYHA, New York Heart Association; EF, ejection fraction.
showed no wall motion recovery (contractile reserve at
in eight of them. During exercise ECHO six of these 13 patients
cardiac vein in five of them and in a postero-lateral cardiac vein
lateral myocardial infarction: the LV lead was placed in a lateral
Thirteen patients enrolled in this study had a previous postero-
Viability of postero-lateral wall
during multivariable linear regression analysis (Table 3
was independently associated with the improvement after CRT
P
13/21, 62%,
35% vs. 8/21, 38%,
P
¼
0.91). Moreover, neither rest nor exercise MR
were considered as future non-responders), the
overall predictive value of exercise ECHO to CRT response
reached 92% (59/64).

Figure 2 Rest intraventricular dyssynchrony was not predictive
of a reverse left ventricle (LV) remodelling after cardiac resyn-
chronization therapy (CRT) (A), whereas the presence of exer-
cise dyssynchrony was predictive of a significant LV end-systolic
volume reduction after CRT (B). Considering only postero-lateral
infarctions, patients with the LV lead matching with a postero-
lateral scar (no viability during stress echocardiography) had a sig-
nificant worsening of end-systolic LV volumes compared to
patients with echo-stress viability (C). LV dyssynchrony was evalu-
ated using the maximal difference of electromechanical delay
among four LV basal segments, cut-off ≥ 65 ms.

Figure 3 Rest intraventricular dyssynchrony was only slightly
predictive of ejection fraction (EF) recovery after cardiac resyn-
chronization therapy (A), whereas exercise dyssynchrony was
much more predictive (B). Considering only postero-lateral
infarctions, patients with the left ventricle (LV) lead matching
with a postero-lateral scar (no viability during stress echocardio-
graphy) had a significant worsening of EF compared to patients
with echo-stress viability (C). LV dyssynchrony was evaluated
using the maximal difference of electromechanical delay among
four LV basal segments, cut-off ≥ 65 ms.

Table 2 summarizes sensitivity, specificity, and predictive values
of rest and peak exercise intraventricular dyssynchrony. The pre-
dictive value of rest dyssynchrony for CRT response was only
70%, whereas predictive value of exercise LV dyssynchrony was
89%. This difference was statistically significant (P = 0.01). Exercise
dyssynchrony was better related with functional and ECHO
improvement than rest dyssynchrony (Figures 2–4). Moreover,
only exercise LV dyssynchrony was an independent predictor of
CRT response during multivariable linear regression analysis
(Table 3). Figure 5 shows the different electro-mechanical delays
at rest and during exercise of the LV basal segments.

Mitral regurgitation
A colour-Doppler jet area > 7 cm² was considered the cut-off for
moderate/severe MR: no difference was observed between
responder and non-responder patients either for rest MR (15/43,
35% vs. 8/21, 38%, P = 0.97), or for exercise MR (26/43, 60% vs.
13/21, 62%, P = 0.91). Moreover, neither rest nor exercise MR
was independently associated with the improvement after CRT
during multivariable linear regression analysis (Table 3).

Viability of postero-lateral wall
Thirteen patients enrolled in this study had a previous postero-
lateral myocardial infarction: the LV lead was placed in a lateral
cardiac vein in five of them and in a postero-lateral cardiac vein
in eight of them. During exercise ECHO six of these 13 patients
(46%) showed no wall motion recovery (contractile reserve at
any step of exercise at least of one of the four segments of the
mid or basal posterior and lateral wall), thus indicating transmural
scar. In all these six patients, the LV lead position matched with a
non-viable segment, being all the four postero-lateral segments
non-viable. All these six patients were non-responders and had
no improvement after CRT, according to a recent MRI study.20
In the other seven patients (54%) exercise stress echocardiography
showed a postero-lateral contractile reserve: in six of them there
was viability both in lateral and posterior wall (at least one segment
for each wall) and therefore the LV lead matched with a viable wall;
in one patient there was viability in the lateral wall and no viability
in both segments of the posterior wall. In this last patient, the
LV lead matched with a viable segment because it was in the lateral
vein. All the seven patients with matching between viability and
LV lead positioning also had exercise LV dyssynchrony and were
responders at 6-month follow-up. When compared with the pre-
vious six patients without viability, the seven patients with match-
ing between viability and LV lead position had a significantly higher
EF improvement after CRT (Δ:+9.5 ± 4.3 vs. −2.8 ± 2.7%, P <
0.001), a significantly higher positive LV remodelling (Δ end-systolic
LV volume in percentage: −18.1 ± 12.3 vs. +10.1 ± 11.0%, P <
0.001) and a significantly higher functional improvement at 6-min
walking test (Δ: +59 ± 74 vs. +13 ± 33 m, P = 0.1) (Figures 2
and 3). When these data were added to LV dyssynchrony evalua-
tion (all patients with the LV lead in a postero-lateral scar
without viability were considered as future non-responders), the
overall predictive value of exercise ECHO to CRT response
reached 92% (59/64).
Functional improvement

The 6-min walking test, performed before and 6 months after CRT, was used to assess the functional improvement. The six patients with LV lead in a postero-lateral cardiac vein and postero-lateral infarction without viability at stress ECHO had the worst results showing no functional improvement after CRT ($D: +13 \pm 33$ m).

The analysis of LV dyssynchrony in the remaining 58 patients showed that the 44 patients with exercise dyssynchrony had a significantly greater improvement than those (14 patients) without exercise dyssynchrony ($D: +108 \pm 99$ vs. $+10 \pm 79$ m, $P = 0.001$), whereas the 38 patients with rest dyssynchrony had similar functional improvement of the 20 patients without rest dyssynchrony ($+83 \pm 103$ vs. $+86 \pm 105$ m; $P = 0.93$) (Figure 4).

Resynchronization at 6 months follow-up

By comparison of rest and exercise TDI at baseline and at 6 months follow-up, a significant LV resynchronization occurred in responder patients, whereas a worsening of LV synchrony both at rest and during exercise occurred in non-responders. Looking at rest TDI ECHO, the reduction of rest LV dyssynchrony from baseline to 6 months follow-up was significantly greater in responder than in non-responder patients ($2\Delta 76 + 80$ ms, $P = 0.01$). However, this difference was much more significant when considering exercise LV dyssynchrony ($2\Delta 76 + 93$ ms, $P < 0.001$).

Discussion

CRT is considered a major breakthrough in the treatment of patients with drug-refractory HF. Recent large-scale randomized trials have convincingly demonstrated that CRT has beneficial effects on HF symptoms, LV function, and survival. However, up to 40% of patients do not respond to CRT, thus emphasizing the need for better selection criteria. The presence of intraventricular dyssynchrony, regardless of QRS duration, seems to be the principal determinant of CRT effectiveness, although disappointing results were observed in the PROSPECT...
different catheter positioning during CRT implantation.

Exercise echo dyssynchrony

The role of exercise LV dyssynchrony in DCM is not yet clear. The main benefit from CRT is the improvement of the functional class. This usually happens shortly after CRT, before a LV positive remodelling occurs. This latter usually takes place in a longer time frame (months). We therefore hypothesized that dyssynchrony during exercise may play an important role in determining the functional improvement in HF patients. A recent study showed that exercise may dramatically change the presence and extent of ventricular dyssynchrony in HF patients; some patients develop ventricular dyssynchrony during exercise, whereas others have resynchronization on exercise, and it correlates with cardiac output and MR changes. \(^\text{15}\) Figure 5 shows that exercise also induces a spatial change in the electro-mechanical delay of the LV: the lateral wall became more delayed at rest but during exercise the posterior wall became more delayed. As reported in a previous study, it is possible that pacing in the region of most severe mechanical delay will provide the best results of CRT and hence a lower non-responder rate. \(^\text{22}\) As mechanical delays are different during rest and exercise, it may be useful to detect exercise mechanical delay for a different catheter positioning during CRT implantation.

This study is the first to show that the presence of LV dyssynchrony at rest is not the most important determinant of response to CRT: indeed, exercise dyssynchrony was the greatest predictor of response to CRT. Rest dyssynchrony showed poor results similarly to the PROSPECT study, with an overall predictive value of 70%, whereas exercise dyssynchrony yielded a predictive value of 89% \((P = 0.015)\). Moreover, the functional improvement at follow-up assessed by 6-min walking test behaved the same way with respect to exercise LV dyssynchrony \((P = 0.001)\); on the contrary, rest LV dyssynchrony could not predict the functional improvement at follow-up \((P = 0.93)\). The benefit in LV remodelling at the 6-month follow-up were significantly greater in patients with exercise LV dyssynchrony (Figure 2). Multivariable linear regression analysis showed that exercise LV dyssynchrony was the single independent predictor of improvement after CRT (Table 3).

**Figure 5** This figure underlines the fact of how exercise induces a spatial change in the electro-mechanical delay of the left ventricle basal segments: the basal posterior segment becomes more delayed during exercise when compared with rest \([\text{latest activated only in 17% of patients (11/64) at rest and in 31% of patients (20/64) during exercise}\]
whereas the basal lateral segment becomes less delayed during exercise \([\text{latest activated segment in 45% of patients (29/64) at rest and only in 33% of patients (21/64) during exercise}\]
IVS denotes interventricular septum.

**Postero-lateral infarction**

Bleeker et al. \(^\text{20}\) have recently reported that patients with postero-lateral transmural scar have a very low response rate (14%) to CRT owing to an ineffective LV resynchronization, in contrast to a favourable response to CRT (81%) of patients without transmural postero-lateral scar. In that study, transmural scar tissue was evaluated with contrast-enhanced MRI \((\geq 50% \text{ of LV wall thickness = transmural postero-lateral scar})\). The detection of contractile reserve using provocative tests, such as stress ECHO, can differentiate transmural from non-transmural scar too, whereas rest ECHO is not able to show viability when akinesia is present. In our study, in the 13 patients with a previous postero-lateral infarction, the LV lead was placed in a lateral cardiac vein (five patients) or in a postero-lateral cardiac vein (eight patients). In seven of 13 patients, the LV lead position matched with a viable segment with contractile reserve at stress ECHO, whereas in six of 13 patients, the LV lead position matched with a non-viable segment (transmural scar). All the seven patients with the LV lead in a viable segment also had exercise LV dyssynchrony and were responders at 6-month follow-up, whereas the other six patients were all non-responders and showed a statistically significant worsening of EF and LV end-systolic volumes at 6-month follow-up (Figures 2 and 3). The overall predictive value of exercise ECHO for CRT response increased to 92% when these data were added to exercise dyssynchrony evaluation (patients with the LV lead positioned in a segment without viability were considered future non-responders). Therefore, exercise stress ECHO seems to be able to replace MRI in assessing postero-lateral scar transmurality, being less expensive and more commonly available. Moreover, in patients with a transmural scar limited to the posterior or to the lateral wall, the effect of a different LV lead positioning with a matching between the cardiac vein (lateral vs. postero-lateral) and the viable LV wall (lateral vs. posterior) may be important to avoid ineffective LV pacing. However, these data need further confirmation owing to the small sample size of this subgroup of patients.

**Resynchronization at 6-month follow-up**

Looking at resynchronization during follow-up, it appears that exercise resynchronization plays a more important role than rest resynchronization in LV reverse remodelling. In fact, rest...
resynchronization was less improved in responders ($P = 0.01$) compared with exercise resynchronization ($P < 0.001$). This aspect also strengthens the predictive role of exercise ECHO.

**Study limitations**

Since our echo equipment was not able to simultaneously detect TDI velocities in several LV segments, dysynchrony of the LV was evaluated by detecting single pulse wave TDI velocities and delays in each LV basal segments. The recently published PROSPECT study showed disappointed predictive values for CRT response of complex colour TDI method assessed at rest, and the authors refer to it the high variability of TDI measures noted in the study. The PROSPECT did not evaluate exercise dysynchrony and did not assess viability of LV postero-lateral wall as performed in this study, and the predictive values were low for all the various methods used. However, in the PROSPECT, the best predictive value for LV end-systolic volumes reduction after CRT was achieved by the easiest colour TDI method of the time difference between lateral and septal peak systolic velocity (only two walls assessed) probably because the lower variability of this method. In our study, we used the single pulse wave TDI to evaluate dysynchrony, which is easy to detect. Moreover, the single pulse wave TDI has a higher frame rate of colour TDI. Therefore, we chose to use the single pulse wave TDI because a high temporal resolution is crucial for LV dysynchrony assessment, especially at the high heart rates reached during exercise. Probably for these reasons we had low variability of pulse wave TDI measures. However, a direct comparison of pulse wave TDI and colour TDI assessed during exercise was not performed.

Finally, to ensure that rest and exercise ECHO predictive values were not related to the TDI method used, we decided to compare two different TDI methods to evaluate LV dysynchrony: the maximum delay between peak systolic velocities among four walls within the LV with a cut-off of 65 ms, and the SD among peak systolic velocities of six basal segments of LV with a cut-off of 32. The first method was validated by Bax in a large cohort of patients, the second method is similar to the method validated by Yu and is the one with the highest predictive value for CRT response up to now. In our study, the two methods had an agreement for exercise LV dysynchrony of 98%, meaning that the study results were independent of the TDI method used.

**Conclusions**

Exercise intraventricular dysynchrony, assessed during exercise TDI ECHO, is a strong predictor of CRT response, significantly superior to rest intraventricular dysynchrony (89 vs. 70%, $P = 0.015$). It was the only parameter independently associated with LV reverse remodelling after CRT at multivariable analysis ($P < 0.001$) and was clearly superior to rest LV dysynchrony in predicting functional improvement at 6 min walking test. Exercise resynchronization at follow-up was significantly greater than rest resynchronization in ECHO responders, strengthening the role of exercise resynchronization for LV reverse remodelling. Exercise ECHO was also able to differentiate postero-lateral infarction with or without myocardial viability (contractile reserve), and this allowed a matching between LV lead positioning and myocardial viability useful to predict CRT response. When these data were added, the overall predictive value of exercise ECHO reached 92%.

The literature shows that one-third of patients fail to respond to CRT. In our study, in which CRT was implanted following the current guidelines, we had similar results with 33% (21/64) of non-responder patients. Exercise TDI ECHO showed an overall predictive value for CRT response of 92%. It could therefore be used to improve selection criteria for patients who are candidates for CRT, thus reducing the frequent inappropriate implantation of biventricular pacemakers.

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**References**


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**CARDIOVASCULAR FLASHLIGHTS**

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Disappearing left atrial mass with drainage of pericardial effusion

Kian Keong Poh1,2,3*, Eric Chong1,2,3, and Tiong Cheng Yeo1,2,3

1Cardiac Department, National University Hospital, 5 Lower Kent Ridge Road, Level 3, Main Building, Singapore 119074; 2National University Heart Centre, Singapore; and 3Yong Loo Lin School of Medicine, National University of Singapore, Singapore

* Corresponding author. Tel: +65 923 732 89, Fax: +65 687 229 98, Email: doctorpoh@yahoo.com

A 25-year-old female with history of intravenous drug abuse was admitted with tricuspid valve infective endocarditis. Echocardiogram demonstrated a large vegetative mass (arrow) in the right atrium (RA) (Panels A and B). She underwent excision of the mass, pericardial reconstruction of the tricuspid valve with Kay annuloplasty, and was discharged. A month later, she presented acutely in shock with severe metabolic acidosis and respiratory distress. Physical examination revealed muffled heart sounds; chest X-ray showed cardiomegaly. She was intubated and resuscitated. Echocardiography revealed a large pericardial effusion (PE) with fibrin deposits adherent to the epicardium. A mobile ring-shaped mass (echodensity with echolucent centre; arrow-head) with independent motion was documented in the left atrium (LA) (Panels Cand D). The differential diagnoses included localized tamponade or recurrent endocarditis with left atrial involvement. Emergent pericardiocentesis was performed. Large amount of serous fluid were drained, with immediate resolution of the atrial mass. Despite intensive support, the patient died on the same day. Autopsy revealed extensive fibrous pericardial adhesions to the epicardium, most prominently at the upper third pericardial space and posteriorly. No vegetation was detected in the valves or heart chambers. Subsequent pericardial fluid and blood culture did not reveal any growth of organisms. Post-cardiac surgical pericardial adhesions may contribute to localized tamponade of the relatively lower pressure atrium, mimicking mass on echocardiography.

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