Cardiac resynchronization therapy: left or left-and-right for optimal symptomatic effect—the LOLA ROSE study

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Introduction

Cardiac resynchronization therapy (CRT) is established as an effective treatment for heart failure patients who remain symptomatic despite maximum tolerated drug therapy.1,2 Selection of patients has been based on prolongation of the QRS complex as an indicator of abnormal ventricular activation and a predictor of increased mortality.3,4 The significance of dyssynchronous ventricular contraction, as is seen with left bundle branch block, has been extensively studied.3,5–7 In CRT, resynchronization of right ventricular (RV) and left ventricular (LV) contraction better simulates optimum physiological activity and as a result improves cardiac output.8–10 There are however other potential mechanisms of benefit—these include improvement in intraventricular synchrony, reduction in pre-systolic mitral regurgitation, and improvement in diastolic function through prolongation of ventricular filling time.1,11 Large-scale trials of atrial-synchronized biventricular (BiV) pacing have been performed in patients with a combination of sinus rhythm, heart failure symptoms, reduced LV ejection fraction (LVEF), prolongation of the QRS complex (usually due to left bundle branch block), and optimized medical therapy. These studies have demonstrated improvements in New York Heart Association (NYHA) class, exercise tolerance, quality of life, and survival.10,12–15

The acute haemodynamic and energetic benefits associated with BiV pacing are also found with pacing of the left ventricle in isolation: such left univentricular (LUV) pacing has resulted in improvements in cardiac output, systolic blood pressure, and pulmonary capillary wedge pressure similar to those seen with BiV pacing.16–18 As with BiV pacing, LUV pacing has been shown to improve cardiac function at diminished energy costs.19 However, there are clear differences between the two modalities of pacing in terms of electrical activation and echocardiographic mechanics. Experimental work has demonstrated that LUV pacing improves mechanical synchrony despite increased electrical dispersion based on epicardial activation mapping.20 Clinical echocardiographic studies have shown that LUV pacing improves LVEF, reduces mitral regurgitation, and improves LV intraventricular synchrony to a degree similar to that seen with BiV pacing.21 However, LUV pacing is associated with longer pre-ejection duration and interventricular conduction delay and shorter transmural filling times than BiV pacing.21 Uncertainty persists as to whether these differences may have important functional consequences, for example on exertion, when faster heart rates may make diastolic filling time more critical, and in terms of chronic

Aims Biventricular (BiV) pacing and left univentricular (LUV) pacing can each produce clinical benefits in heart failure. The impact of modern refinements in pacing optimization on the relative benefits of these two modes is unknown. We aimed to compare these two modes in patients with heart failure, using Echo-based optimization of each pacing mode.

Methods and results Paired data were collected on 18 patients (age 72 ± 8 years; 16 male) with refractory heart failure symptoms, sinus rhythm, and LBBB with QRS duration > 120ms. Patients were randomized to an initial 8 weeks of either BiV or LUV pacing, followed by 8 weeks of the other mode, in a blinded cross-over design. Echocardiography was used to optimize atrioventricular delay for both modes and right ventricular–left ventricular offset for BiV mode. Peak oxygen consumption (baseline 13.6 ± 2.7; BiV 15.8 ± 3.0; LUV 15.2 ± 3.1mL/kg/min), 6 min walk distance (baseline 258 ± 47; BiV 290 ± 63; LUV 287 ± 69m), and scores on SF36 health questionnaire (baseline 41.5 ± 16.8; BiV 56.8 ± 19.6; LUV 51.8 ± 21.3) did not differ between BiV and LUV modes. New York Heart Association class was significantly better in BiV than in LUV mode (P < 0.01).

Conclusion In this pilot study, we found no differences in major clinical outcome measures between the two modes of resynchronization.
LV remodelling and sustained improvement in clinical indices.

The evolution of pacing technology now allows LV and RV leads to be programmed independently. Greater adjustment of pacing parameters is therefore possible, with adjustment of both atrioventricular (A-V) and interventricular (V-V) delays, yielding further haemodynamic improvements. Whether these translate into clinical benefits remains unclear. We therefore designed the LOLA ROSE trial to examine whether optimized atrial-synchronized sequential BiV pacing was superior to optimized atrial-synchronized LUV pacing in terms of patient symptoms and exercise capacity.

Methods

The LOLA ROSE study received approval from the local Ethics Committee and complied with the Declaration of Helsinki. Study subjects gave informed consent.

Patient selection and study entry criteria

Patients were recruited from those scheduled to undergo BiV pacemaker insertion at the Royal Sussex County Hospital, Brighton, UK. Implantation criteria (based on the UK national guidelines) were NYHA Class III/IV heart failure despite maximal tolerated medical therapy, QRS duration on ECG ≥ 120ms, and LVEF of 35% or less. Further inclusion criteria (for this study) were sinus rhythm, left bundle branch block, and qualitative Echo evidence of LV dyssynchrony. Exclusion criteria were age < 18 years, pregnancy, inability to give informed consent or to perform the functional assessments, and planned insertion of a combined BiV/ICD device. No drug treatment changes were planned during the study period, although it was acknowledged that diuretic doses might require adjustment.

Study design

The study had a randomized, cross-over design as shown in Figure 1, as employed in previous studies of CRT, such as MUSTIC and PATH-CHF. Block randomization was used for the allocation of the first pacing mode used, to ensure balanced assignment of subject numbers to each group. Patients were blinded to pacing mode throughout the study to reduce bias.

Outcome measures

The primary endpoint was peak oxygen consumption. This was derived from cardiopulmonary exercise testing using a bicycle ergometer with an established ramp protocol for use in heart failure. Secondary endpoints were distance achieved in 6min walk test, score on SF-36 health questionnaire, NYHA class, and patient’s preferred mode of pacing.

Implantation details

Patients in the study were implanted with either Medtronic (Minneapolis, MN, USA) InSync III or Guidant (St. Paul, MN, USA) Contak Renewal TR systems, according to operator preference. Pacing leads were inserted through standard subclavian and cephalic vein approaches. The RV lead tip was placed in the apex of the right ventricle. The LV lead tip was placed in the posterolateral cardiac vein where possible or in an alternative posterior or lateral vein. The location chosen for LV lead was that giving the greatest spatial separation from the tip of the RV lead, with stable LV capture and without diaphragmatic capture at four times threshold voltage.

Pacing modes and echocardiographic optimization of parameters

Two modes of pacing were under comparison in this study:

(i) BiV mode: atrial-synchronized, sequential BiV pacing, with optimized A-V and RV–LV (V-V) delays;
(ii) LUV mode: atrial-synchronized, LUV pacing, with optimized A-V (atrio-LV) delay.

Optimization of pacing intervals was performed in the following manner. A baseline transthoracic echocardiogram was performed at the follow-up visit within 2 weeks of implantation, with the device inactivated. Using the apical four-chamber view, the mitral inflow Doppler profile was used to measure the velocity of the early (E) and late (A) waves and assess the deceleration time of the E wave, the mitral velocity time integral, and the total transmitral filling time as a percentage of the cycle length. Mitral regurgitation was quantified using colour flow Doppler and continuous wave Doppler.

Left ventricular outflow tract diameter was measured in the parasternal long-axis view. Cardiac output was assessed using the LV outflow tract velocity time integrals from apical five-chamber views. The myocardial performance index (Tei index) was also calculated from the time interval between A-wave cessation and the onset of the following E wave on mitral inflow Doppler (apical four-chamber view) and the aortic ejection time (apical five-chamber view). All measurements were taken at rest with the patient in the left lateral position and were recorded onto s-VHS videotape. Measurements were taken over three consecutive sinus beats and values averaged. Following randomization, the echocardiographic protocol was repeated and the device was then optimized.

The atrio-LV delay was programmed first. This was set so as to maximize diastolic LV filling, with no truncation of the transmitral A wave while ensuring paced ventricular activation. With LUV pacing, no further optimization could take place. With BiV pacing, the pacing delay between RV and LV stimulation was systematically varied and the RV–LV offset producing maximal cardiac output was utilized.

Statistics

The use of a cross-over design necessitates evaluation of both carry-over effects and period effects. This was performed using standard statistical methods for each of the outcome measures. The two pacing modes under study were then compared using a matched pairs t-test for those outcome measures which were continuous variables. For NYHA scores, non-parametric testing was performed (the distribution of intra-subject differences in NYHA scores between the two modes was assessed after dividing subjects into two groups based on which mode they received in the first period; the distribution of these differences within the two groups was then
compared using a Mann–Whitney test). For patient preference of pacing mode (a secondary endpoint), two-sided sign tests were performed. These tests were carried out using the software SAS (release 8.02) by an independent statistician.

Results

Patient flows

Twenty-three patients were recruited and randomized into the study between March 2004 and November 2005. One patient was withdrawn following unsuccessful transvenous insertion of the coronary sinus lead (and subsequently underwent successful epicardial LV lead placement). One patient withdrew from the study after the first period of pacing (BiV in her case), having experienced a marked symptomatic improvement and being unwilling to risk any deterioration by switching to a different pacing mode. One patient presented with decompensated heart failure after implantation but prior to first optimization and was programmed open-label to BiV pacing. One patient developed pneumonia, deteriorated clinically, and was withdrawn from the study. One patient developed marked recurrence of heart failure symptoms in his second period of pacing (LUV mode in his case) and therefore underwent unplanned early switch-back to BiV mode, without assessments being performed in LUV mode. Hence, 18 patients completed study assessments in both pacing modes and they form the basis for the following analyses. Baseline demographic and clinical data for these patients are shown in Table 1.

Of these 18 patients, 9 patients were randomized to BiV pacing first and the other 9 were randomized to LUV first. One patient was relatively intolerant of LUV pacing and another was relatively intolerant of BiV pacing—they therefore underwent functional assessments before the completion of the respective 8 week periods. Table 2 indicates the echocardiographically optimized pacing parameters for each mode of pacing and the resulting values of echocardiographically assessed cardiac output and myocardial performance index (Tei index) upon commencement of pacing at these optimized parameters.

Clinical outcome measures

Table 3 shows a comparison of outcome measures between BiV vs. baseline, LUV vs. baseline, and BiV vs. LUV. It can be seen that both pacing modes produced (expected) improvements, relative to baseline, in both primary and secondary outcome measures. Individual subjects’ data for the primary outcome measure are shown as a scattergram in Figure 2, emphasizing inter-individual variations in the response to CRT.

There was no difference between BiV and LUV for the primary endpoint, peak oxygen consumption. With regard to the secondary outcome measures, BiV pacing is associated with a significantly better NYHA score than LUV pacing but no other differences were found.

Patients’ preference of pacing mode was studied. One of the 18 patients expressed no preference for either mode and felt no symptomatic improvement from pacing. Of the remaining 17 patients, 12 preferred BiV pacing and 5 preferred LUV pacing. However, this does not represent significant evidence of an overall preference for BiV pacing ($P = 0.14$). The picture is further complicated once the order of testing is taken into account. All the patients who received BiV pacing first preferred it; of those who received LUV pacing first, one expressed no preference and five of the remaining eight preferred LUV pacing. There is a suspicion that patients tended to favour the mode used in the first period of pacing, irrespective of which mode it was (probably because the difference between baseline and either mode of CRT is more noticeable to most patients than the more subtle difference between modes).

Limitations of study

Our study involved a relatively small number of patients. With regard to the primary endpoint, a formal calculation of the achieved power indicates that this data set would provide a 72% power to detect a difference of 2mL/kg/min between the two modes. The 95% confidence interval for the estimated difference between the two pacing modes, in terms of the peak VO$_2$, extends beyond 1mL/kg/min in

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**Table 1** Patient demographics

<table>
<thead>
<tr>
<th>Age (mean ± SD)</th>
<th>72.2 ± 8.3 years</th>
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<tbody>
<tr>
<td>Gender</td>
<td>16 males:2 females</td>
</tr>
<tr>
<td>Aetiology of heart failure (n = 18)</td>
<td>Ischaemic heart disease 14, Dilated cardiomyopathy 4</td>
</tr>
<tr>
<td>Intrinsic QRS duration (ms) (median, range)</td>
<td>160, 140–190</td>
</tr>
<tr>
<td>Drug treatment (n = 18)</td>
<td>ACE-inhibitor or All receptor blocker 17, Beta blocker 7, Loop diuretic 15, Aldosterone receptor blocker 9</td>
</tr>
<tr>
<td>NYHA class at baseline (n = 18)</td>
<td>II 1, III 15, IV 2</td>
</tr>
</tbody>
</table>

QRS, QRS complex on electrocardiogram; ACE, angiotensin-converting enzyme; All, angiotensin II; NYHA, New York Heart Association.

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**Table 2** Optimized parameters for biventricular and left univentricular pacing

<table>
<thead>
<tr>
<th></th>
<th>BiV pacing</th>
<th>LUV pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimum A-V delay (ms) (median, range)</td>
<td>100, 80–150</td>
<td>100, 80–120</td>
</tr>
<tr>
<td>Optimum RV-LV delay (ms) (median, range)</td>
<td>16, 44 to –20</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cardiac output (litres/min) (mean ± SD)</td>
<td>4.5 ± 1.1</td>
<td>4.8 ± 1.8 ($P = 0.53$)</td>
</tr>
<tr>
<td>Tei index (mean ± SD)</td>
<td>0.68 ± 0.36</td>
<td>0.65 ± 0.35 ($P = 0.92$)</td>
</tr>
</tbody>
</table>

BiV, biventricular; LUV, left univentricular; A-V, atrioventricular; RV, right ventricular; LV, left ventricular.
favour of BiV mode. This latter value is considered a clinically relevant threshold\textsuperscript{31,32}; hence our study did not achieve sufficient power to exclude confidently a potentially relevant advantage to BiV (over LUV) in the order of 1 to 1.9\,mL/kg/min. Since the 95\% confidence interval extended only to 0.63\,mL/kg/min in favour of LUV mode, a clinically relevant advantage to LUV (over BiV) for this outcome measure is unlikely.

The cross-over design of the study raises the issue of potential carry-over and/or period effects. We applied statistical tests for carry-over for all comparisons for each clinical outcome measure. For none of the comparisons was there any statistically significant evidence of carry-over. There was a suspicion of an effect of period for the secondary outcome measure 'patient’s preferred mode of pacing', as discussed earlier. The only other measure for which testing for period effect produced a statistically significant result was the 6min walk distance, when comparing LUV against baseline. The $P$-value for this test was 0.048, in favour of the second period; however, this borderline result was felt likely to have arisen by chance, particularly in view of the lack of significant period effect for any other outcome measures when comparing LUV to baseline.

Table 3: Objective assessment of functional differences between baseline, biventricular pacing, and left univentricular pacing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline (mean ± SD)</th>
<th>BiV (mean ± SD)</th>
<th>LUV (mean ± SD)</th>
<th>$P$-value, BiV vs. baseline</th>
<th>$P$-value, LUV vs. baseline</th>
<th>$P$-value, BiV vs. LUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak (\text{VO}_2) (mL/kg/min)</td>
<td>13.6 ± 2.7</td>
<td>15.8 ± 3.0</td>
<td>15.2 ± 3.1</td>
<td>0.008</td>
<td>0.033</td>
<td>0.21</td>
</tr>
<tr>
<td>SF36 score</td>
<td>41.5 ± 16.8</td>
<td>51.8 ± 19.6</td>
<td>51.8 ± 21.3</td>
<td>0.005</td>
<td>0.071</td>
<td>0.17</td>
</tr>
<tr>
<td>6 min walk distance (m)</td>
<td>258 ± 47</td>
<td>290 ± 63</td>
<td>290 ± 47</td>
<td>0.001</td>
<td>0.061</td>
<td>0.93</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0</td>
<td>2.5</td>
<td>1.9</td>
<td>0.006</td>
<td>0.014</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Figure 2: Scattergram showing individual subjects' data for primary endpoint (peak \(\text{VO}_2\)) at baseline, in BiV mode, and in LUV mode.

Discussion

This is the first randomized study comparing optimized LUV pacing with optimized sequential BiV pacing in patients with heart failure. No difference was seen in the major primary and secondary clinical outcome measures.
that it became significant only at rates of 140 bpm in that relations was shown between the two modes but the fact randomized comparative study. They did not find any 33 patients who underwent LUV or BiV pacing in a non-anical delay than BiV pacing.21 However, a number of studies pacing results in a greater degree of interventricular mech- between the two modes is unclear. For example, LUV cardiographic parameters which show greater differences after second period (regardless of order of pacing modes used).

LUV pacing also produces longer aortic pre- reduced by CRT actually matters in practice remains uncer- hence, whether the degree to which this variable is useful in predicting the response of patients to CRT; 21,33–35 LUV pacing produces longer aortic pre-ejection times and shorter transmitial filling times than BiV pacing.21 This may become important particularly at faster heart rates. In keeping with this hypothesis, Vollman et al.36 recently demonstrated that pacing the heart at increasing rates led to differences emerging between the two modes—at higher heart rates, an enhancement in LV dP/dt (compared with baseline rate) was seen with BiV but not with LUV pacing. They also found that, at the highest heart rates, BIV pacing was associated with lower LV end-diastolic pressures and greater LV systolic pressures than LUV pacing. Thus a difference in the force–frequency relations was shown between the two modes but the fact that it became significant only at rates of 140 bpm in that study may limit its importance in most settings.

Existing comparisons of biventricular and left univentricular pacing

Touiza et al.37 examined 6 month clinical outcomes in 33 patients who underwent LUV or BiV pacing in a non-randomized comparative study. They did not find any significant difference between the two modes with regard to NYHA class, 6 min walk distance, peak VO₂. However, optimization of cardiac output, with respect to A-V delay (not possible in atrial fibrillation) or RV/LV offset (not available at the time), was not a feature of this study. Hence extrapolation of their results to a contemporary BIV pacing population in sinus rhythm is difficult.

Auricchio et al.41 studied heart failure patients in sinus rhythm and compared the effects of LUV vs. simultaneous BIV pacing, 4 weeks in each mode, in a randomized cross-over design trial. In their study, the LV pacing site was accessed via a thoracotomy and epicardial placement of the LV lead. The RV and LV leads were connected to separate pacing systems and hence there was no facility for varying offset between pacing in the two ventricles. They identified no difference between the two modes in terms of NYHA class, 6 min walk distance, peak VO₂, or QOL score.

Most recently, the BELIEVE Investigators42 recruited patients in LBBB, who were being implanted with CRT-defibrillator devices, into a parallel arm trial comparing BIV and LUV pacing. The primary endpoint (‘response’ to CRT) was a composite of improvement in LVEF and/or 6 min walk. In their study, 4 weeks in each mode, in a randomized cross-over design trial. In their study, the LV pacing site was accessed via a thoracotomy and epicardial placement of the LV lead. The RV and LV leads were connected to separate pacing systems and hence there was no facility for varying offset between pacing in the two ventricles. They identified no difference between the two modes in terms of NYHA class, 6 min walk distance, peak VO₂, or QOL score.

Interpretation of LOLA ROSE results

This work was intended as a pilot study comparing the two modes of CRT in the modern era of optimization. We have not shown any definitive clinical difference between these modes. Although there was a statistically significant difference between the two modes in terms of NYHA class, none was found for SF-36 scores. This probably reflects the different clinical emphases of the two scoring systems and a greater subjectivity (on the part of the assessor) with NYHA scores. Hence we would not wish to infer a superiority of BiV mode on the basis of this isolated positive finding.

Hence the results of our study are in keeping with those from the PATH-CHF I trial.37 This is despite several methodo- logical differences which reflect the change in clinical prac- tice over the intervening time—for example, in the method of LV pacing employed and the use of optimization tech- niques for both A-V and V-V delay in our study. Percutaneous BiV lead placement is now the method of choice for CRT in most centres and hence our study reflects contemporary practice. The clinical benefits of optimizing
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V–V offset (in addition to A–V delay) have not yet been fully resolved, although the non-randomized InSync III study and the RHYTHM II ICD study have suggested that it might be smaller than expected at six months’ follow-up.²⁴,⁴⁶ On going studies (DECREASE-HF and B-LEFT-HF) should help clarify unresolved issues with regard to the relative benefits of alternative modes of CRT delivery.⁴⁵,⁴⁶

Acknowledgements

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Conflict of interest: none declared.

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