Right ventricular lead positioning does not influence the benefits of cardiac resynchronization therapy in patients with heart failure and atrial fibrillation

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Aims
Little is known about the optimal right ventricular (RV) pacing site in cardiac resynchronization therapy (CRT). This study compares bi-ventricular pacing at the left ventricular (LV) free wall combined with two different RV stimulation sites: RV outflow tract (RVOT+LV) vs. RV-apex (RVA+LV).

Methods and results
Thirty-three patients (32 males) with chronic heart failure, NYHA class III–IV, optimal drug therapy, QRS-duration ≥150 ms, and chronic atrial fibrillation (AF) received CRT with two different RV leads, in the apex (RVA) or outflow tract (RVOT), together with an LV lead, all connected to a bi-ventricular pacemaker. Randomization to pacing in RVOT+LV or RVA+LV was made 1 month after implantation and cross-over to the alternate pacing configuration occurred after 3 months. The median age of patients was 69 ± 10 years, the mean QRS was 179 ± 23 ms, and 58% of patients had ischaemic heart disease. Seven patients had pacemaker rhythm at inclusion and 60% were treated with atrioventricular-junctional ablation before randomization. In the RVA+LV and RVOT+LV pacing modes, 67 and 63% (nonsignificant) responded symptomatically with a decrease of at least 10 points in the Minnesota Living with Heart Failure score. The secondary end-points (6-min walk test, peak oxygen uptake, N-Terminal fragment of B-type Natriuretic Peptide, and left ventricular ejection fraction) showed significant improvement between baseline and CRT, but not between RVOT+LV and RVA+LV.

Conclusion
In this randomized controlled study, the exact RV pacing site, either apex or outflow tract, did not influence the benefits of CRT in a group of patients with chronic heart failure and AF. ClinicalTrials.gov ID: NCT00457834.

Keywords
Congestive heart failure • Cardiac resynchronization therapy • Lead placement • Atrial fibrillation • Right ventricular pacing configurations • Cardiac resynchronization • Biventricular pacing • Left ventricular pacing • Right ventricular pacing

Introduction
Cardiac resynchronization therapy (CRT) improves symptoms, ventricular performance, quality of life (QoL), and survival in patients with heart failure, low ejection fraction (EF), and prolonged QRS durations.1,2 The effect of the right ventricular (RV) pacing site on the clinical outcome of CRT remains questionable. Trials have shown that RV apical (RVA) pacing results in left ventricular (LV) dyssynchrony, particularly in patients with pre-existing ventricular dysfunction.3,4 Although the safety and reliability of RV outflow tract (RVOT) pacing are well documented,5 little is known about whether it adds any additional symptomatic benefit to CRT patients, compared with RVA pacing. There were concerns that RVOT pacing might affect myocardial perfusion; yet, this hypothesis was refuted in a small study which...
compared the effect of the two RV pacing sites. In this study, we prospectively compared LV + RVA pacing with LV + RVOT pacing in a randomized fashion in a group of patients with heart failure and atrial fibrillation (AF) to assess any additional beneficial effects on CRT.

Methods

Study design

This was a single-centre randomized double-blind cross-over trial comparing the effects of the two RV pacing sites, RVA and RVOT, in patients receiving CRT. To minimize the number of implanted pacing leads only patients with chronic AF were included. This approach also removed the need for optimizing AV-synchrony. The study was approved by the local ethics committee of Umeå University and all patients gave informed consent before inclusion.

Inclusion criteria

Patients between 18 and 80 years of age with chronic AF were eligible for the study. All patients had (i) chronic heart failure, New York Heart Association (NYHA) class III–IV despite at least 1 month of optimal pharmacological treatment; (ii) a QRS-duration of ≥150 ms or were chronically paced; and (iii) LV ejection fraction (LVEF) ≤35% as assessed by echocardiography. Patients were excluded if they had a conventional indication for pacemaker (patients already on chronic pacemaker treatment could be included) or heart failure not related to systolic dysfunction or a cardiac ischaemic event within the previous month.

Implantation

All implantations were performed by the same medical team at the Heart Centre, Umeå University Hospital. The pacemaker used was InSync III (Medtronic Inc., Minneapolis, MN, USA). Conventional bipolar screw-in electrodes were placed in the RVA and RVOT.
The RVOT lead was introduced under fluoroscopic guidance through the pulmonary valve and withdrawn with a counterclockwise movement to a position beneath the valve. The position of the lead was checked in the left anterior oblique position in which it pointed posteriorly. We aimed to see a positive QRS deflection in leads II, III, and aVF. The LV lead was positioned in a lateral or posterolateral site, guided by a coronary sinus venogram. A Y-connector (5866-38M, Medtronic Inc., Minneapolis, MN, USA) was connected to the LV pacemaker channel to bifurcate the anode and the cathode of the bipolar output. The RVA lead was connected to the anodal port of the Y-connector and the LV lead to the cathodal port of the Y-connector. The RVOT lead was connected to the RV pacemaker channel. This arrangement allowed simultaneous unipolar stimulation of LV and RVA ([bipolar mode from the LV port through the Y-adapter, with the RV port (to the RVOT) turned off] or LV and RVOT [unipolar mode from the LV port through the Y-adapter to the LV lead with the RV port (RVOT) turned on], as well as separate determination of pacing thresholds (Figures 1 and 2). The atrial pacemaker port was plugged since all patients were in AF. In cases where attempts to place the LV-electrode failed, a second attempt was made within 1 month. If re-operation was necessary, the ongoing follow-up period was restarted after surgery.

Follow-up

After a run-in period of 1 month, during which the pacemaker was programmed to VVI at 30 beats/min, the intrinsic ventricular rate was assessed using 24 h Holter monitoring and an exercise test. Patients with ≥85% ventricular pacing were randomized in the study. Those with <85% pacing underwent AV-junctional ablation and were randomized 1 month after ablation. The patients were randomized to either LV+RVA pacing or LV+RVOT pacing. After 3 months, the pacemaker was programmed to the alternate pacing configuration for another 3-month period (Figure 3). During the active pacing periods the pacemaker was programmed to VVIR at a base rate of 70–80/min. and the upper sensor-driven rate was 120/min. The pacing thresholds were determined at follow-up 1, 4, and 7 months after implantation and at least 100% marginal was programmed, except in two patients with high pacing thresholds in whom a lower safety marginal was accepted. All patients underwent the following examinations at baseline and 3 and 6 months after randomization: QoL assessment with the Minnesota Living with Heart Failure Questionnaire (MLWHF), 6 min walk test (6MWT), peak oxygen uptake by exercise test (pVO2), 2D and Doppler echocardiography, and N-Terminal fragment of B-type Natriuretic Peptide (NT-proBNP) analysis. A research nurse performed all pacing programming, but the rest of the researchers were blinded to the actual pacing configuration. The primary endpoint was QoL assessed by the MLWHF Questionnaire; with the responders defined as having a symptomatic improvement of at least 10 points. The secondary end-points were: 6MWT, peak VO2, NT-proBNP, and LVEF.

Statistics

Continuous data are presented as mean values ± SD (range) except when noted. Group comparisons of continuous data were made using the Wilcoxon rank-sum test. Group comparisons of discrete data were made using the $\chi^2$ test. Cases with cell counts less than five were examined by the Fisher exact probability test. All statistical tests were two-tailed and $P < 0.05$ was regarded as significant.

Results

Thirty-two male and one female patient were included in this study, whose baseline characteristics are presented in Table 1. Three patients did not complete the study (two died and one needed a heart transplantation) before the end of the two randomization periods. Seven patients were chronically paced at inclusion due to conventional bradycardia; one had previously

Figure 3 Study design. Randomization to pacing in RVOT+LV or RVA+LV was made 1 month after implantation and cross-over to the alternate pacing configuration occurred after 3 months.
undergone AV-junctional ablation. In accordance with the study protocol 18 patients underwent AV-junctional ablation before randomization due to a high intrinsic heart rate during the run-in period (mean resting heart rate was 76 beats/min). Seventeen patients were randomized to LV+RVA pacing in the first instance and 16 patients to LV+RVOT pacing in the first instance. One patient required re-programming of the pacemaker to the previous pacing configuration (LV+RVA) 2 months after cross-over. This patient underwent functional assessment before re-programming and was evaluated in the study.

Pacemaker performance and complications

Implantation was successful in all patients. One patient required two attempts to place the LV lead. Four patients needed re-operation due to LV lead dislodgement (1), RVA lead dislodgement (1), defective Y-connector (1), and revision of the pulse generator pocket (1). The stimulation threshold remained stable during the follow-up period and the LV threshold was comparable with RVA and RVOT leads over time (Table 2). During follow-up four patients had symptoms related to phrenic nerve stimulation which in all cases could be resolved with a minor re-programming.

Clinical response

A total of 23 of 33 patients enrolled in the study responded (Responders) symptomatically to CRT pacing, having achieved a decrease of at least 10 points in the MLWHF Questionnaire. The remaining 10 patients did not achieve enough scoring and hence were considered as Non-Responders. There was no difference between the Responders and Non-Responders in any of the baseline demographics or measurements of ventricular function (Table 1). In the group as a whole, LV+RVA pacing and LV+RVOT resulted in significant improvements in primary and secondary outcome measures compared with baseline (Table 3). Both LV+RVA and LV+RVOT groups significantly improved in 6-min walked distance with a mean increase of 45 ± 46.
RV lead positioning does not influence the benefits of CRT

(P < 0.001) and 34 ± 48 metres (P = 0.001), respectively, compared with baseline. Peak oxygen uptake also increased by 0.133 ± 0.210 L/min (P = 0.002) in the LV+RVA group and 0.106 ± 0.209 L/min (P = 0.007) in the LV+RVOT group and NT-proBNP decreased in both groups by 1198 ± 1821 ng/L (P = 0.005) and 1043 ± 1719 (P = 0.002), respectively. Left ventricular ejection fraction increased by 7.9 % (P = 0.020) in the LV+RVA group and 6.5 % (P = 0.002) in the LV+RVOT group. However, no significant differences were found between the LV+RVA and LV+RVOT patients, in the primary end-point MLWHF score or any of the secondary end-points (Table 3). Thirteen of the 18 patients (72%) who underwent AV-junctional ablation improved on intermediate-term follow-up of CRT in patients with chronic heart failure and AF. We found the RV pacing site, apex or outflow tract, did not make any difference to the beneficial response of CRT in this modest size cohort of patients. In addition, our results show a satisfactory response of two-third of patients with heart failure and AF to CRT, irrespective of the RV pacing site.

**Discussion**

This is the first prospective randomized study to investigate the impact of RVOT lead positioning and conventional RVA pacing on the benefits of CRT.

**Table 2 Lead thresholds in V (pulse width 0.4 ms) at implant and follow-up**

<table>
<thead>
<tr>
<th>Lead type</th>
<th>Implant</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-lead (cathodal)</td>
<td>0.98 ± 0.88</td>
<td>1.32 ± 1.39</td>
<td>1.28 ± 1.10</td>
<td>1.57 ± 1.94</td>
</tr>
<tr>
<td>RVA-lead (anodal)</td>
<td>0.64 ± 0.59</td>
<td>1.81 ± 0.75</td>
<td>1.88 ± 1.33</td>
<td>2.04 ± 1.25</td>
</tr>
<tr>
<td>RVOT-lead</td>
<td>0.47 ± 0.20</td>
<td>0.69 ± 0.31</td>
<td>0.78 ± 0.31</td>
<td>0.76 ± 0.32</td>
</tr>
</tbody>
</table>

LV-lead, left ventricular lead; RVA-lead, right ventricular apical lead; RVOT-lead, right ventricular outflow tract lead.

**Table 3 Primary and secondary effect variables**

<table>
<thead>
<tr>
<th></th>
<th>Baseline, n = 33</th>
<th>RVOT + LV vs. baseline, n = 30</th>
<th>LV + LV vs. baseline, n = 28</th>
<th>RVOT + LV vs. RVA + LV, n = 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLWHF</td>
<td>44 ± 18</td>
<td>−16 (P &lt; 0.001)</td>
<td>−20 (P &lt; 0.001)</td>
<td>−1 (P = 0.939)</td>
</tr>
<tr>
<td>6-min walk test (m)</td>
<td>326 ± 114</td>
<td>+34 (P = 0.001)</td>
<td>+45 (P &lt; 0.001)</td>
<td>−2 (P = 0.389)</td>
</tr>
<tr>
<td>VO₂ max (L/min)</td>
<td>1.16448 ± 0.299</td>
<td>+0.106 (P = 0.007)</td>
<td>+0.133 (P = 0.002)</td>
<td>−0.019 (P = 0.509)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>4606 ± 3174</td>
<td>−1043 (P = 0.002)</td>
<td>−1198 (P = 0.005)</td>
<td>+164 (P = 0.349)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23 ± 7</td>
<td>+6.5 (P = 0.002)</td>
<td>+7.9 (P = 0.002)</td>
<td>−1.5 (P = 0.386)</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>195 ± 62</td>
<td>−9.9 (P = 0.206)</td>
<td>−7.7 (P = 0.143)</td>
<td>−2.2 (P = 0.936)</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>152 ± 56</td>
<td>−15.7 (P = 0.049)</td>
<td>−18.0 (P = 0.017)</td>
<td>2.3 (P = 0.284)</td>
</tr>
<tr>
<td>LVSV (mL)</td>
<td>53 ± 13</td>
<td>+5.5 (P = 0.115)</td>
<td>+8.3 (P = 0.045)</td>
<td>−2.8 (P = 0.531)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0 ± 0.2</td>
<td>−0.4 (P &lt; 0.001)</td>
<td>−0.4 (P = 0.001)</td>
<td>0.0 (P = 0.414)</td>
</tr>
</tbody>
</table>

MLWHF: Minnesota Living with Heart Failure Questionnaire; VO₂ max, maximal oxygen uptake; NT-proBNP, N-Terminal fragment of B-type Natriuretic Peptide; RVOT, right ventricular outflow tract; LV, left ventricle; RVA, right ventricular apex; LVEF, left ventricular ejection fraction; LVED, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; NYHA, New York Heart Association.

**LV + RVA vs. LV + RVOT pacing**

Conventional pacing and CRT pacing involve inserting a lead in the RV apex. Such mode of electrical stimulation of the RV has been previously reported to cause asynchronous septal motion which has implications on overall LV performance. To rectify this potential complication RVOT pacing has been envisaged as a means of minimizing the mechanical asynchrony and hence improving the LV function. The results of this approach, in the literature however, are not consistent. Patients paced for bradycardia as well as those needing acute pacing, have shown a measurable haemodynamic benefit from RVOT pacing over RVA pacing.6–11 Long-term studies, for similar indications, however, failed to report any consistent advantage in using RVOT over RVA pacing.6,12–15 Furthermore, acute CRT studies in heart failure patients, comparing different RV pacing sites, have shown improvements in haemodynamic variables, but with no overall advantage of a specific pacing site.16 Our results of long-term CRT in AF, heart failure, and left bundle branch block are in line with previously published long-term observational studies which did not demonstrate any favourable benefit from RVOT over RVA pacing.17–19 In view of the above, one may even argue whether pacing the right ventricle in the setting of CRT is of any benefit, at all since conventional RVA pacing did not result in any symptomatic difference when compared with RVOT pacing. This speculation is supported by Leclercq et al. who in dogs with heart failure and LBBB found 25% increase in dP/dt max, aortic pulse pressure in both bi-ventricular pacing and LV-pacing and by an observational study and a randomized study which showed a significant 12-month improvement of EF with LV pacing, comparable to that with biventricular pacing.20–22 Two ongoing trials (B-LEFT HF and
DCREASE-HF) in patients with CRT may eventually answer the question whether isolated LV pacing is sufficient to obtain the optimal clinical benefit.\textsuperscript{2,3,24}

**Study limitations**

We randomized the patients 1 month after pacemaker implantation or 1 month after AV-junction ablation. The latter may have contributed to clinical improvement by optimizing the ventricular rate and filling time. The pacing configuration in present study gave anodal stimulation of RVA during RVA+LVOT pacing. In RVOT+LV pacing both sites were stimulated cathodally. In experimental studies\textsuperscript{26} as well as in a clinical setting,\textsuperscript{26} anodal pacing of left ventricle was associated with signs of immediate improvement in mechanical function of the left ventricle, compared with cathodal pacing. The effect is presumably mediated through initial activation of larger volume of myocardium and increased conduction velocity, compared with conventional cathodal pacing. A similar, long-term improvement related to anodal pacing of RVA in the RVA+LV combination may in our study have obscured a possible beneficial effect of RVOT-pacing in the RVOT+LV combination. We raised doubt about the real benefit of RV pacing in the setting of CRT in heart failure; however, we did not test this provocative suggestion with isolated LV pacing.

**Conclusion**

The results of this trial do not justify changing the standard site of RV pacing from apical to outflow tract in patients receiving CRT for heart failure. In addition, our trial confirms the beneficial effect of resynchronization therapy in two-third of patients with AF, irrespective of the RV pacing site.

**Conflict of interest:** None of the authors have conflicts of interests to disclose.

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**References**