Cardiac resynchronization therapy in pacemaker-dependent patients with left ventricular dysfunction

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Received 23 February 2013; accepted after revision 2 May 2013; online publish-ahead-of-print 4 June 2013

Aims
Heart failure and left ventricular (LV) systolic dysfunction (LVSD) are common in patients with permanent pacemakers. The aim was to determine if cardiac resynchronization therapy (CRT) at the time of pulse generator replacement (PGR) is of benefit in patients with unavoidable RV pacing and LVSD.

Methods and results
Fifty patients with unavoidable RV pacing, LVSD, and mild or no symptoms of heart failure, listed for PGR were randomized 1:1 to either standard RV-PGR (comparator) or CRT. The primary endpoint was the difference in change in LV ejection fraction (LVEF) between RV-PGR and CRT groups from baseline to 6 months. Secondary endpoints included peak oxygen consumption, quality of life, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. At 6 months there was a difference in change in median (interquartile range) LVEF [9 (6–12) vs. 2.1 (–4.5 to –0.8)%; P < 0.0001] between the CRT and RV-PGR arms. There were also improvements in exercise capacity (P = 0.007), quality of life (P = 0.03), and NT-proBNP (P = 0.007) in those randomized to CRT. After 809 (729–880) days, 17 patients had died or been hospitalized (6 in CRT group and 11 in the comparator RV-PGR group) and two patients in the RV-PGR arm had required CRT for deteriorating heart failure. Patients with standard RV-PGR had more days in hospital during follow-up than those in the CRT group [4 (2–7) vs. 11 (6–16) days; P = 0.047].

Conclusion
Performing CRT in pacemaker patients with unavoidable RV pacing and LVSD but without severe symptoms of heart failure, at the time of PGR, improves cardiac function, exercise capacity, quality of life, and NT-pro-BNP levels.

Keywords
Left ventricular dysfunction • Pacemaker • Heart failure

Introduction
The treatment of bradycardia by implantation of an artificial cardiac pacemaker is a routine procedure associated with extended longevity for patients with atrioventricular (AV) block,¹,² and improved quality of life for those with sick sinus syndrome.³ However, long-term right ventricular (RV) pacing is associated with adverse remodelling of the left ventricle (LV),⁴ which can contribute to or cause left ventricular systolic dysfunction (LVSD) or overt heart failure.⁵–⁹ In patients with cardiovascular co-morbidity and a higher proportion of ventricular paced beats, the rate of LVSD is 60%, and subsequent annual mortality or hospitalization rate is 12%.¹⁰ Since the recognition that RV pacing is associated with an adverse prognosis,¹¹ algorithms have been developed to reduce RV pacing in patients in whom it is avoidable,¹²–¹⁷ but these are of little use in patients with complete AV block or atrial fibrillation with a slow ventricular response. Patients with severe heart failure and an existing RV pacemaker are therefore often offered an ‘upgrade’ to cardiac resynchronization therapy (CRT) as an extra procedure. Although longitudinal studies have suggested that patients upgraded to CRT have a similar response in terms of symptoms and cardiac function as patients with intrinsic left bundle branch block,¹⁸ there are no randomized data supporting this approach. Only one randomized study of CRT for heart failure included patients with previous devices, and subgroup analysis
What’s new?

- Pacemaker patients with left ventricular systolic dysfunction (ejection fraction <50%), unavoidable right ventricular (RV) pacing (>80%), but few symptoms of heart failure requiring a pulse generator replacement (PGR), benefit from cardiac resynchronization therapy in terms of cardiac function, exercise capacity, quality of life, and N-terminal pro-B-type natriuretic peptide levels.
- Cardiac resynchronization therapy implanted opportunistically at the time of PGR might be cost-effective by reducing hospitalization rates and the need for further procedures as a result of deteriorating heart failure.

suggested no benefit from CRT.\textsuperscript{19} Despite this, upgrade procedures represent a quarter of all CRT implants in Europe.\textsuperscript{25}

In patients with a standard RV pacemaker, the time of pulse generator replacement (PGR) is an infrequently realized opportunity to assess and optimize patients’ medical and device therapy.\textsuperscript{27} Doing so will identify patients with important LVSD but few symptoms.\textsuperscript{11} Whether to implant an LV lead in these patients at the time of PGR is unknown but such an approach might improve symptoms, avoid infection risk of additional future procedures, and be cost-effective by preventing future heart failure events, optimizing generator use and reducing the number of subsequent reoperations.

The aim of this study was to establish the clinical effects of elective CRT vs. standard PGR (comparator group) in patients with unavoidable RV pacing, LVSD and few or no symptoms of heart failure requiring PGR for battery depletion.

Methods

We recruited consecutive adult patients listed for routine RV pacemaker PGR due to battery depletion,\textsuperscript{11} with unavoidable RV pacing (>80% in the preceding 12 months), LVSD [left ventricular ejection fraction (LVEF) <50%], and mild or no symptoms of heart failure, into a 1 : 1 randomized controlled trial of pacemaker upgrade to CRT vs. continued RV pacing (comparator group). Exclusion criteria included life-threatening or severe co-morbidity (severe chronic airways disease or terminal malignancy), poor non-invasive imaging quality, recent hospitalization for heart failure, ventricular dysrhythmias, and inability or unwillingness to provide consent. The study is registered on the Clinical Trials website as NCT01652248.\textsuperscript{22}

Each subject underwent echocardiography, a blood draw for renal function, blood count and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement, filled in a quality-of-life questionnaire, and, in those capable, a cardiopulmonary exercise test was performed to document peak oxygen consumption (pVO\textsubscript{2}). Subjects were randomized by random number generation to receive either a standard RV-PGR or CRT.

Cardiac resynchronization therapy or RV-PGR was undertaken within 2 weeks of consent. In patients randomized to CRT upgrade, venous access, coronary sinus cannulation, and LV lead placement were undertaken as the standard practice, aiming for a lateral position of the LV lead electrodes and the leads were connected to a Medtronic Insync III or Consulta P generator (Medtronic). This was then programmed to be the standard practice, aiming for a lateral position of the LV lead electrodes and the leads were connected to a Medtronic Insync III or Consulta P generator (Medtronic). This was then programmed to

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Our primary endpoint was the change in LVEF from baseline to 6 months between the two groups. Echocardiographic images were recorded on a Vivid 9 imaging system and stored offline on a commercially available analysis system (Echopac, GE). Follow-up images were anonymized and analysed in random fashion at the end of the study by a single-blinded observer (J.G.). Left ventricular ejection fraction was calculated using the modified Simpson’s rule (bi-plane). Based upon our previous observational work,\textsuperscript{19} and randomized trials of CRT,\textsuperscript{23} we estimated a difference in mean LVEF of 5% at 6 months. In our sample size calculation, we allowed for an LV lead implant failure rate of around 8%, and a loss to follow up of 5%. In order to have a power of 90% in a two-sided independent samples t-test to detect the 5% difference we calculated that we would need to recruit 50 patients (25 to each arm).

Secondary endpoints were exercise capacity measured by peak oxygen consumption (pVO\textsubscript{2}), quality of life, and NT-proBNP levels. Peak oxygen consumption was calculated from the last 30 s of a symptom-limited incremental peak exercise test on a treadmill or stationary cycle, using breath-by-breath analysis (Medgraphics). Since our enrolment criteria excluded patients with severe symptoms of heart failure, we did not use the New York Heart Association classification, expecting most to be in either class I or II. Instead, to measure quality of life, we used the EuroQol-HF questionnaire,\textsuperscript{27} which is sensitive to change in symptoms\textsuperscript{25,26} and relates to outcomes in chronic heart failure (CHF). For ease of analysis, quality-of-life scores from the EuroQol-HF were converted to a percentage of the maximum expected. We also pre-specified an exploratory combined endpoint of all-cause hospitalization and all-cause mortality until follow-up of all patients was complete using hospital and general practice records.

Baseline variables are reported as means (95% confidence intervals). Analysis of baseline and follow-up data was undertaken on an intention-to-treat basis. Outcome variables were not normally distributed or equally variable so we employed a non-parametric approach using two sided Wilcoxon rank sum tests. We corrected for multiple testing using the false discovery rate.\textsuperscript{27} The study was approved by Leeds West Local Research Ethics Committee and Research and Development at Leeds Teaching Hospitals NHS Trust.

Results

Baseline characteristics for the enrolled patients can be seen in Table 1. Pacing indication was complete heart block in all but five patients, whose baseline indication was sick sinus syndrome but who had subsequently developed AV conduction disease. Patients randomized to CRT had a higher mean radiation dose and a longer procedural time than those receiving an RV-PGR (Table 2). There were no peri-procedural or early complications, and to date there have been no long-term complications. In the CRT arm, there was one failure due to superior vena cava stenosis. This patient received RV-PGR, but as per our pre-specified analysis plan, was included in the CRT arm for the analysis.

Table 3 shows the changes from baseline to 6 months in patients randomized to CRT upgrade or RV-PGR. In the CRT group there was an improvement in LV function (Figure 1A and B). In patients randomized to CRT there was also an improvement in peak exercise capacity, a reduction in NT-proBNP levels and an improvement in quality of life. There was no heterogeneity in any of the four outcomes.
Cardiac resynchronization therapy in patients with pacemakers

Table 1 Baseline variables

| Variable                              | CRT (n = 25) | RV (n = 25) |
|---------------------------------------|-------------|-------------|
| Age (years)                           | 77 (73–81)  | 77 (73–81)  |
| Sex (male)                            | 16          | 16          |
| Height (cm)                           | 164 (156–172) | 166 (162–170) |
| Weight (kg)                           | 82 (74–90)  | 73 (67–80)  |
| Remote MI (n)                         | 5           | 6           |
| Remote CVA (n)                        | 1           | 1           |
| Hypertension (n)                      | 14          | 10          |
| Diabetes mellitus (n)                 | 4           | 7           |
| CABG (n)                              | 6           | 7           |
| Heart rate (b.p.m.)                   | 77 (71–83)  | 68 (62–74)  |
| DBP (mmHg)                            | 66 (70–62)  | 71 (65–77)  |
| SBP (mmHg)                            | 120 (110–130) | 139 (125–153) |
| Sinus rhythm (n)                      | 20          | 17          |
| QRS duration (ms)                     | 168 (160–176) | 159 (149–169) |
| Years of pacing (years)               | 10 (8–12)   | 12 (10–14)  |
| Baseline pacing indication (CHB)(n)   | 22          | 23          |
| Beta-blocker (n)                      | 14          | 13          |
| ACE inhibitor (n)                     | 18          | 19          |
| Warfarin (n)                          | 5           | 6           |
| Quality of life (%)                   | 82 (76–88)  | 87 (83–91)  |
| Creatinine (μmol/L)                   | 117 (107–127) | 119 (105–133) |
| Estimated GFR (l/min)                 | 56 (50–62)  | 55 (49–61)  |
| Haemoglobin (g/dL)                    | 13.6 (13.0–14.2) | 13.4 (12.6–14.2) |
| B-type natriuretic peptide (pmol/L)   | 1613 (570–2656) | 977 (471–1483) |
| LVEF (%)                              | 39 (35–43)  | 41 (37–45)  |
| LVEDD (mm)                            | 50.6 (47.7–53.5) | 49.2 (46.2–52.1) |
| PAP (mmHg)                            | 34 (28–40)  | 33 (29–37)  |
| pVO2 (ml/kg/min)                      | 14.2 (12–16) | 15.8 (13–18) |

Values are mean (confidence interval).

Table 2 Implant data

| Variable                     | CRT (n = 25) | RV (n = 25) |
|------------------------------|-------------|-------------|
| Implant duration (min)       | 66 (54–78)  | 51 (43–59)  |
| Fluoroscopy time (min)       | 12.2 (6.3–18.4) | 1.3 (0.4–2.1) |
| Dose (mGy)                   | 2578 (1214–3942) | 298 (102–494) |

Values are mean (confidence interval).

Table 3 Changes in outcomes variables between groups from baseline to 6 months

| Variable                        | CRT (n = 25) | RV (n = 24) | P value |
|---------------------------------|-------------|-------------|---------|
| ΔLVEF (%)                       | 9 (6)       | −1.5 (5.3)  | <0.0001 |
| ΔpVO2 (ml/kg/min)               | 2.1 (2.5)   | −0.5 (2.0)  | 0.007   |
| ΔQuality of life (%)            | 2.3 (11.4)  | −2.0 (3.5)  | 0.007   |
| ΔNT-proBNP (pmol/L)             | −56 (763)   | 85 (554)    | 0.03    |

Values are median (interquartile range).

Discussion

Upgrade to CRT at the time of pacemaker PGR in patients with unavoidable high RV pacing and LVSD leads to clinically and statistically significantly improved LV function, quality of life, and exercise capacity, and reductions in N-terminal pro-B-type natriuretic peptide levels. This strategy was associated with fewer all-cause hospitalizations and fewer subsequent interventions, and, if this pattern is reproduced in larger studies, might therefore be particularly cost-effective.

Heart failure or asymptomatic LVSD is a common finding in patients with permanent pacemakers and is associated with a poor overall outcome, particularly in patients requiring a high amount of ventricular pacing. What constitutes optimal management of pacemaker-associated LVSD has never been formally proven. Many of the trials of medical and device therapy for CHF have excluded patients with pacemakers, and in those that did not, the numbers have been insufficient to warrant a subgroup analyses. Specifically, CRT that improves cardiac function, symptoms and prognosis in CHF patients and is indicated (class I recommendation, level of evidence A) for patients with LVSD (LVEF ≤35%), ongoing or previous symptoms (NYHA class III and IV) and conduction delay, has hitherto not been the focus of a randomized controlled study in patients with RV pacemakers.

been hospitalized for any cause (6 in CRT group and 11 in the RV-PGR group). Mean (CI) days in hospital was 8 (4–12) days, with a trend to fewer days in hospital in those randomized to CRT than those receiving standard PGR [4 (2–7) vs. 11 (6–16) days; P = 0.047]. Two patients in the RV-PGR were upgraded to CRT for deteriorating heart failure within this extended follow-up period.

with respect to baseline atrial rhythm, with patients in atrial fibrillation demonstrating an improvement in cardiac function, exercise capacity, BNP, and quality of life from baseline, of similar magnitude to the changes seen in patients with sinus rhythm. The only variable to behave differently by atrial rhythm was delta LV end-diastolic diameter (LVEDD), which did not change in patients with sinus rhythm but was significantly reduced by CRT in patients with atrial fibrillation (P = 0.019). Hence although CRT was associated with a reduction in LVEDD overall, this did not reach statistical significance for the group as a whole.

Mean duration of extended follow-up at the censor date of 1 May 2012 was 809 (729–880) days. During this time three patients had died, one in the CRT arm and two in the RV-PGR arm. Our combined exploratory endpoint of death or all-cause hospitalization was not statistically different between the arms: 17 patients had died or...
Observational studies have suggested that upgrading RV pacing systems to CRT in patients with CHF leads to similar improvements in cardiac function and symptoms as de novo CRT implants. and international guidelines discuss briefly the potential to upgrade existing devices to CRT as part of the management of severe CHF but admit that there are no data to support such a strategy. Despite the lack of randomized data, CRT upgrades to existing pacemaker systems are commonly undertaken in Europe and the USA. The European data suggest that upgraded patients seem to have comparable symptom and mortality outcomes and complications further than performing a de novo implant, due to potential limited venous access, risks of damage to old leads and infection. In the second cross-over study discussed above, 5 of the 36 patients enrolled needed further procedures (including one thoracotomy) to achieve LV pacing. In the ‘Resynchronization–defibrillation for ambulatory heart failure trial’ (RAFT), which randomized patients listed for implantable cardioverter defibrillator but without severe heart failure symptoms to a standard defibrillator or a CRT-defibrillator, patients with previous pacemakers did not benefit from CRT, even if their QRS duration was greater than 200 ms. It cannot therefore be assumed that in a patient with severe CHF associated with an existing pacemaker upgrading to CRT is beneficial.

Preliminary randomized, controlled data in patients with LV dysfunction requiring treatment of bradycardia demonstrated better LV function with CRT vs. RV pacing. The recently reported ‘Biventricular versus right ventricular pacing in heart failure patients with atrioventricular block’ (BLOCK HF) study suggests benefits of CRT over RV pacing on a combination of all-cause mortality, heart failure hospitalization, and deterioration in LV function in patients with mild LVSD requiring a pacemaker for AV block. However, the study reported much higher complication rates than would be expected with standard RV pacing, and since all patients received a CRT device, whether this approach is clinically or cost-effective vs. carefully programmed RV pacing might remain unanswered.

The present study, presents the first randomized, placebo controlled data on how to manage patients with an existing standard pacemaker, requiring a generator replacement found to have LVSD and mild symptoms of heart failure. De novo CRT in patients with mild symptoms, LVSD and conduction delay reduces hospitalizations, so the present results not only bridge gaps in knowledge about CRT in patients with standard pacemakers, but also provide further data about patients with mild symptoms of heart failure. It does so by proposing a strategy that might, in some patients, avoid additional procedures with their attendant risk, and the cost of further surgery and wasted pacemaker generators. If our preliminary data suggesting reduced hospitalizations is reproduced in subsequent studies, this strategy might be particularly cost-effective.

Limitations

The present study is an important proof of concept study but warrants further robust efficacy and cost effectiveness evaluation. Limitations of the current study include that it was performed at a single centre, patients and the study physician were unblinded, and the endpoints reported are surrogates for prognosis. However, the images used to produce the data for the primary endpoint were collected by a single experienced echocardiographer blinded to study allocation and then reported in random order at the end of follow-up with dates and patient identifiers removed. The disadvantage of surrogate endpoints is typical of proof-of-concept small-scale studies, and LV ejection fraction has appropriately come under particular scrutiny in CRT studies recently as a poor marker for outcome, but the change in each of our endpoints including exercise capacity and quality of life was consistent and our extended follow-up data hint at benefits on hard outcomes that would require a larger study or longer follow-up to confirm.

Conclusions

Heart failure is a common co-morbidity in patients with permanent pacemakers and is related to hospitalization and mortality, but
since patients with pacemakers were often excluded from studies of treatments for heart failure, whether medical or device intervention is of benefit is unknown. The present data demonstrate that LVSD in the presence of unavoidable RV pacing responds to CRT and that the time of PGR might be an opportunity to optimize pacing prescription. Further evaluation of whether a coordinated programme of risk stratification, careful device prescription, optimal programming and optimized medical therapy for pacemaker-associated LVSD could lead to improved outcomes and cost-effective patient care is warranted in this patient group.

Conflict of interest: none declared.

Funding
This research project was made possible through an unrestricted research grant from Medtronic UK.

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Non-invasive electrophysiological imaging of acute rejection in a transplanted heart

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Case report

We present the first case of non-invasive cardiac electrophysiological mapping using electrocardiographic imaging (ECGI) of a 51-year-old man with acute cellular rejection 9 months after cardiac transplantation. He had moderate right ventricular (RV) systolic dysfunction and global left ventricular (LV) dysfunction (LVEF 40–45%) on echocardiogram, which progressed to cardiogenic shock requiring biventricular assist device (BiVAD) support. He had complete right bundle branch block (RBBB) on baseline ECG after transplantation, with a QRS duration (QRSd) of 140 ms, that prolonged to 200 ms on Day 3 of hospitalization (9 months post-transplant) and returned to baseline (126 ms) a month later. Panel A shows the ECGI isochrone map on Day 1 of rejection, showing early activation (asterisks) of the septal RV outflow tract and LV apex, and a line of block along the septum causing delayed RV activation. Panel B shows resolution of the septal line of block a month later, after escalation of immunosuppressive therapy and BiVAD support, with delayed activation over the anterior RV, consistent with the patient’s baseline RBBB. Left ventricular activation was synchronous, while the RV and adjacent septum showed changes in the activation pattern over the course of rejection with changing block lines, indicating greater susceptibility to injury than that of the LV during rejection.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/non-invasive-imaging-transplanted-heart.pdf