Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study

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Aim
Chronic right ventricle (RV) apical (RVA) pacing is standard treatment for an atrioventricular (AV) block but may be deleterious to left ventricle (LV) systolic function. Previous clinical studies of non-apical pacing have produced conflicting results. The aim of this randomized, prospective, international, multicentre trial was to compare change in LV ejection fraction (LVEF) between right ventricular apical and high septal (RVHS) pacing over a 2-year study period.

Methods and results
We randomized 240 patients (age 74 ± 11 years, 67% male) with a high-grade AV block requiring >90% ventricular pacing and preserved baseline LVEF. To receive pacing at the RVA (n = 120) or RVHS (n = 120). At 2 years, LVEF decreased in both the RVA (57 ± 9 to 55 ± 9%, P = 0.047) and the RVHS groups (56 ± 10 to 54 ± 10%, P = 0.0003). However, there was no significant difference in intra-patient change in LVEF between confirmed RVA (n = 85) and RVHS (n = 83) lead position (P = 0.43). There were no significant differences in heart failure hospitalization, mortality, the burden of atrial fibrillation, or plasma brain natriuretic peptide levels between the two groups. A significantly greater time was required to place the lead in the RVHS position (70 ± 25 vs. 56 ± 24 min, P < 0.0001) with longer fluoroscopy times (11 ± 7 vs. 5 ± 4 min, P < 0.0001).

Conclusion
In patients with a high-grade AV block and preserved LV function requiring a high percentage of ventricular pacing, RVHS pacing does not provide a protective effect on left ventricular function over RVA pacing in the first 2 years.

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Keywords
Right ventricular apical pacing • Right ventricular high septal pacing • Left ventricular function • Select site pacing

Introduction
Implantation of a permanent cardiac pacemaker remains the only effective treatment for patients with a high-grade AV block. Each year, ~750 000 new pacemakers are implanted worldwide with over a quarter in the USA alone.1 The right ventricular apex (RVA) has been the traditional site for lead placement.2 However, accumulating clinical and experimental evidence suggests that chronic sustained RVA pacing may have a deleterious effect on left ventricular (LV) systolic function in some patients.3–13 These observations have raised interest in pacing sites outside the RVA.7,14–17 Pacing from the right ventricle (RV) septum is felt to provide more physiological LV activation presumably due to its closer proximity to the specialized conduction system.18,19

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However, the results of clinical studies on the chronic effects of alternate site pacing have been conflicting. The DAVID study showed a relationship between the burden of RVA pacing and an increased risk of heart failure-related mortality, although that study only included patients with impaired LV function, an indication for an implantable defibrillator and no requirement for bradycardia pacing. Accumulating clinical and experimental data suggest that pacing at the RVA should be avoided. No randomized large-scale clinical studies comparing non-RVA sites in patients with a high-degree AV block and normal LV function have been conducted to support this hypothesis.

We sought to compare two RV pacing lead positions on LV systolic function with an adequately powered randomized clinical trial over a 2-year period in patients with normal baseline LV function requiring permanent sustained pacing for a high-degree AV block.

Methods

The Protect-Pace study was a randomized, prospective, single-blind multicentre, international trial performed at 18 centres, 10 in the UK, 6 in Australia and 2 in New Zealand between 2007 and 2011 (see Appendix). The study was approved by the Human Research Ethics Committees of participating centres in Australia and New Zealand, and the NRES Committee East Midlands—Nottingham in the UK and was conducted in compliance with the Declaration of Helsinki. All the patients provided written informed consent.

Outcome measures

The primary end-point was intra-patient change in LV ejection fraction assessed by transthoracic echocardiography (TTE). Secondary end-points were death and hospitalization for heart failure, atrial fibrillation (AF), burden, changes in brain natriuretic peptide (BNP) levels, 6-minute walk test, lead placement times, and lead-related adverse events. An independent adverse events advisory committee, blinded to the subject randomizations, adjudicated all deaths, hospitalizations, and serious adverse events.

Patients

Patients were included if they were aged ≥ 18 years or more, with persistent 2:1 AV block or higher and sinus rhythm, scheduled to undergo dual-chamber pacemaker implantation, or with permanent AF and heart block, scheduled to undergo single-chamber ventricular rate-responsive pacemaker implantation in whom the LV ejection fraction was ≥ 40% and there were no clinical signs of heart failure. Patients were excluded if they had: intermittent AV block, reversible causes for AV block, indicated ablation, the requirement for amiodarone therapy within 6 months prior to enrolment, terminal conditions with a life-expectancy of < 2 years, participation in any other study that would confound the results of this study, and pregnant patients or patients who planned to become pregnant during the time-scale of the study.

Study design

This study was a 1:1 randomization of RVA pacing vs. RVHS pacing. Randomization was stratified by centre with randomization codes provided in closed, numbered envelopes at the start of the study. Randomization occurred after informed consent and prior to the start of device implantation. Patients were blinded to the randomization group, but the clinical care teams were not blinded to lead position. All core laboratories were blinded to the pacing site. Echocardiographic data were collected at pre-discharge (baseline) and at 12-, and 24-month follow-up. BNP levels were collected at pre-implant, 12, and 24 months. Patients and device data, including atrial tachyarrhythmia counters, were collected pre-discharge, 6 weeks, 6, 12, 18 and 24 months. A 6-minute walk test was performed at 6 weeks, 12 and 24 months. If pacemaker interrogation revealed < 90% ventricular pacing at the 6-week post-implant visit the patient was withdrawn from the study. Patient demographic and medical history information was collected at enrolment. All prescribed medications were documented, although temporary medications or acute medications used during a medical procedure were not collected.

Echocardiography

Patients were imaged after lying in the resting state for a minimum of 5 min to ensure basal conditions. In the interests of optimizing consistency of imaging, efforts were made to have a single, experienced sonographer to acquire images on all patients at each recruiting centre, using a single designated system (E33, Philips Healthcare, Andover, MA; Vivid 7, e9 or Vivid I, GE Medical Systems, Milwaukee, WI, USA). Recordings were made in end-tidal expiration. Image clips were recorded over three consecutive cardiac cycles, and ectopic and post-ectopic beats were excluded. Images were downloaded to disc and sent to the core laboratory (Cardiovascular Imaging Research group, University of Queensland). To ensure selection of the most comparable images and LV tracings, blinded side-by-side comparison was made of baseline, 12- and 24-month images. LVEF was measured using Simpson’s biplane method, by investigators blinded to pacing site. In situations of poor image quality, EF measurements were supplemented by visual assessment by the echo core lab director.

Procedure for lead placement

Leads were placed in the RVA or RVHS.

Right ventricular apical position

During a standard clinical implant and following randomization, a pacing lead (as chosen by the implanter) was placed inferiorly with the lead tip pointing downwards in the anteroposterior (AP) position. ST segment elevation of the endocardial signal confirmed apposition of the cathode/lead tip to the ventricular myocardium.

Right ventricular high septum

Lead implant was performed using the steerable sheath/lead system (SelectSecure Model 3830, Medtronic, Inc.) by experienced pacing cardiologists/electrophysiologists who were required to have completed a minimum of two successful lead implants. To maximize optimal RVHS position a nine section X-ray grid, designed specifically for this study, was positioned over the fluoroscopy screen during implant procedure in both PA and LAO 40° positions. In all cases, ST segment elevation of the endocardial signal confirmed apposition of the cathode/lead tip to the ventricular myocardium.

Digital fluoroscopic recordings in the AP, 10° right anterior oblique position and the LAO 40° position were made. The following day a digital chest X-ray in the PA and left lateral position were performed and stored to disc. A 12-lead ECG was taken at VVI 90 ppm to achieve 100% ventricular pacing and avoid ventricular fusion.

Time to lead placement was defined as the time from crossing the TV until the lead was placed at its final position.
Analysis of final pacing lead tip position

The Universities of Birmingham, UK and Melbourne, Australia, served as the lead adjudication core laboratories (LAC). The LAC laboratory reviewed all lead positions according to published criteria. Difference in opinion was adjudicated between observers.

Other end-points

The Department of Cardiovascular Sciences, University of Leicester, UK, served as the core laboratory for the NT-proBNP immunoassay. NT-proBNP was evaluated at pre-implant, 12 and 24 months. Blood was obtained by venepuncture under standardized conditions and collected in ethylenediaminetetraacetic acid tubes. Samples were centrifuged at 2000 × g for 20 min at 4°C. Plasma was extracted and stored at −80°C prior to assay which were performed in one batch. NT-proBNP was measured using a non-competitive immunoluminometric assay as previously described. NT-proBNP was measured using a non-competitive immunoluminometric assay as previously described. The lower limit of detection was 0.3 pmol/L. There was no cross-reactivity with ANP, BNP, or C-type natriuretic peptide and inter-assay coefficients of variation were under 3%.

Average AT/AF burden (total minutes in atrial tachyarrhythmia divided by the number of days of follow-up) was calculated for each patient.

Statistical analysis

The study hypothesis was that right ventricular high septal pacing would be superior to apical pacing at preventing LV dysfunction in patients with preserved LV function requiring a high degree of ventricular pacing. An estimated sample size of 172 patients, 86 in each group, was required to detect an absolute difference in LVEF of 5% between two pacing treatment groups at an alpha level of 5% and with a desired power of 90%. No interim efficacy analysis of the data was performed. The study was planned for a 20% data loss over the 2-year follow-up period. Continuous data are presented as mean ± standard deviation (SD) for variables characterized by normal distributions and as median for variables characterized by skewed distributions. Categorical data are presented as count (%). For the AF burden data, a Wilcoxon-Rank-sum test was used to test the difference in the distribution of the average burden between the two study arms.

Data were analysed as intention-to-treat (ITT) according to randomized lead site. Analysis was based on intra-patient changes over time using values at both baseline and 2-year time points. In addition, for the primary outcome a multiple imputation analysis was performed of all patients who had baseline LVEF values, imputing the change in LVEF (baseline-2 year) for patients who did not have a 2-year LVEF value available. The additional analysis was based on characteristics such as age, gender, smoking status, presence of cardiovascular disease or diabetes, height, weight, pre-implant, and 1-year LVEF values for each patient. These values were then used to generate parameter estimates based on a general linear model and the estimates from 20 separate imputations were combined to generate inferences about the model parameters.

A pre-defined subgroup analysis was also performed comparing LVEF in RVA pacing with those patients randomized to the RVHS group in whom the LAC classified the final lead position as septal.

Results

Patient selection

We enrolled 248 patients—as eight exited the study prior to randomization, 240 patients were randomized, 120 to RVA and 120 to RVHS (Figure 1). Eighteen patients (nine from each arm) exited the study at 6 weeks due to failure to meet the percentage ventricular...

Figure 1 Patient flow chart.
pacing criteria and one randomized patient was found to have a missed exclusion criteria and was withdrawn from the study immediately prior to implant. A total of 57 patients exited by the 2-year follow-up (28 RVA, 29 RVHS). Patient characteristics were similar between the two cohorts (Table 1). There was no difference in the number of patients on β-blockers between the two groups [10% at baseline in the RVHS arm and 8% in the RVA arm (P = 0.62) and 19% and 17%, respectively, at 2 years (P = 0.67)].

### Primary objective

In the RVA group, LVEF was 57 ± 9% (n = 104) at baseline and 55 ± 9% at 24 months (n = 88) (P = 0.047). In the RVHS group, LVEF was 56 ± 10% (n = 103) at baseline and 54 ± 10% at 24 months (n = 88) (within group change P = 0.0003) – Figure 2.

In paired data (n = 168), the intra-patient change in LVEF (%) over time was −2.29 ± 10.5 in the RVA group and in the RVHS cohort the intra-patient fall in LVEF was −3.43 ± 8.4 (P = 0.43). A multiple imputation analysis, imputing delta LVEF based on subject characteristics was used to compare the groups, in cases where data were missing. This showed no significant change in LVEF (P = 0.40) by randomization arm.

The mean difference in sequential EF assessments by a single observer was 3 ± 2%, and between two observers was 4 ± 3%.

### Pacing data

At 6 weeks, mean percentage pacing was 99 ± 2% in the RVA group and 99 ± 2% in the RVHS group. At 2 years, the percentage pacing was 98 ± 11 and 93 ± 20%, respectively. In the RVHS group, two patients received <1% pacing at 2 years. The intra-patient change in percentage pacing (2 year—baseline) was not significant between the two study arms (P = 0.089). Seven patients (5.8%) in the RVA group and nine patients (7.5%) had permanent AF at implant (P = 0.6048).

The final lead position is shown in Table 2. One hundred and twenty patients were randomized to the RVHS group, with 118 having leads placed in the true septal position. Of these, 66% were deemed septal by the LAC, 30% were non-septal, 3% had an indeterminate/inconclusive position. A per-protocol analysis was also performed comparing subjects who were randomized to the RVHS and assessed by the LAC as having had the lead placed in the true septal position. In this group, LVEF at baseline was 57 ± 9% in the RVA group and 55 ± 9% at 2 years vs. 56 ± 9 and 54 ± 10% in the RVHS true septal group, respectively (P = 0.34).

### Table 1 Patient characteristics: idiopathic atrioventricular block was defined as no clear clinical cause for atrioventricular block

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>RV apex (n = 120)</th>
<th>RV high-septum (n = 120)</th>
<th>Total patients randomized (n = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.7 (±11.1)</td>
<td>74.7 (±10.0)</td>
<td>74.2 (±10.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73 (60.8)</td>
<td>88 (73.3)</td>
<td>161 (67.1)</td>
</tr>
<tr>
<td>Systemic hypertension (%)</td>
<td>76 (63.3)</td>
<td>67 (55.8)</td>
<td>143 (59.6)</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>39 (32.5)</td>
<td>46 (38.3)</td>
<td>85 (35.4)</td>
</tr>
<tr>
<td>No diagnosed CVS disease (%)</td>
<td>22 (18.3)</td>
<td>26 (21.7)</td>
<td>48 (20.0)</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>27 (22.5)</td>
<td>31 (25.8)</td>
<td>58 (24.2)</td>
</tr>
<tr>
<td>Primary/idiopathic electrical disease (%)</td>
<td>24 (20.0)</td>
<td>21 (17.5)</td>
<td>45 (18.8)</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>4 (3.3)</td>
<td>5 (4.2)</td>
<td>9 (3.8)</td>
</tr>
<tr>
<td>Transient ischaemic attack (%)</td>
<td>3 (2.5)</td>
<td>3 (2.5)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Previous CABG (%)</td>
<td>8 (6.7)</td>
<td>8 (6.7)</td>
<td>16 (6.7)</td>
</tr>
<tr>
<td>Previous valvular surgery (%)</td>
<td>5 (4.2)</td>
<td>4 (3.3)</td>
<td>9 (3.8)</td>
</tr>
<tr>
<td>Indication for implant (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV block—second degree</td>
<td>26 (21.7)</td>
<td>22 (18.3)</td>
<td>48 (20.0)</td>
</tr>
<tr>
<td>AV block—third degree</td>
<td>80 (66.7)</td>
<td>90 (75.0)</td>
<td>170 (70.8)</td>
</tr>
<tr>
<td>Permanent AF at implant</td>
<td>7 (5.8)</td>
<td>9 (7.5)</td>
<td>16 (6.7)</td>
</tr>
<tr>
<td>Right atrial lead implanted</td>
<td>108 (90.0)</td>
<td>104 (86.7)</td>
<td>212 (88.3)</td>
</tr>
</tbody>
</table>

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The effect of right ventricular pacing site on left ventricular function
A significantly greater time was required to place the lead in the RVHS position. For the RVA group, the total implant time was 56 ± 24 min and mean fluoroscopy time was 5 ± 4 min compared with 70 ± 25 and 11 ± 7 min for the RVHS group, respectively (P < 0.0001). Lead dislodgements were not statistically different between the groups (RVA = 2.7%, RVHS 4.5%; n = 0.4987).

### Other end-points

The median of the averaged atrial fibrillation/tachycardia (AT/AF) burden was not statistically significant between the two study arms (RVA n = 90 and RVHS n = 96) (P = 0.226). For RVA patients the mean baseline BNP level (n = 81) was 874.7 ± 899.4 and at 24 months (n = 72) 293.4 ± 348.5 pmol/L. In the RVHS group corresponding BNP levels (n = 77) were 675.5 ± 697.0 and (n = 71) 330.6 ± 414.9 pmol/L, respectively. For subjects who had values at both time points, the mean change in BNP level was −541 ± 770 pmol/L over 2-year follow-up (n = 62) for RVA subjects and −295 ± 578 pmol/L for RVHS subjects (n = 57). The mean change in BNP over 2-year follow-up was not statistically significant between randomization arm (P = 0.053).

There was no statistical difference in 6-minute walk distance (m). For RVA patients with values available at both time points (n = 67), the median distance walked was 389 ± 106.8 m vs. 391.0 ± 127.1 m at 2 years (P = 0.599) and for RVHS patients (n = 68) was 400.3 ± 120.2 and 402.5 ± 115.4 m, respectively (P = 0.736). Data were not available in many cases due to patient mobility issues.

### Death and heart failure hospitalizations

A total of 18 patients died prior to their 2-year follow-up visit, 9 in the RVA group and 9 in RVHS. Cardiac deaths occurred in five RVA group patients (two sudden and three heart failure related) and four RVHS patients (one sudden and three heart failure related). There were 10 instances of hospitalization due to heart failure reported across eight subjects. Six of the subjects with seven hospitalizations were in the RVHS group and the other two subjects who had a total of three hospitalizations were in the RVA group.

### Discussion

The results of this study of patients with preserved baseline LV function indicates that although there was a small reduction in LV systolic function over 2 years in both RVA and RVHS cohorts, there was no significant difference in this change in LV function related to lead position (either on intention-to-treat or adjudicated lead position). This study is the largest randomized study to date comparing traditional RVA to alternate site (RVHS) pacing in pacemaker-dependent patients with a high-degree heart block. Protocol-defined processes were employed to gauge the position of the final pacing lead so that success of true septal lead delivery and placement could be determined.

### Comparison with previous studies

Previous clinical studies randomizing RVA and non-RVA pacing have shown results concerning LV function to have been equivocal. A recent meta-analysis by Shimony et al. concluded that non-RVA pacing generally was not inferior to RVA pacing and that the longer the study period, at least greater than 1 year, the more likely the result would favour non-RVA pacing. They emphasized the difficulties in analysing disparate patient groups and in particular noted the lack of uniform inclusion criteria. Some patients had sick sinus syndrome, and/or AF or high-grade AV block and in many cases the amount of ventricular pacing was variable. A review of individual studies shows that other sources of variation are also important—including duration of follow-up, lead position, percentage pacing, and baseline LV function.

A recent publication with a high degree of ventricular pacing did suggest a benefit on LV systolic function from septal pacing, but only over 1 year of follow-up. Other studies have suggested that changes in LV function might occur after 12–18 months and hence our study was run for 2 years. It is also possible that the 2-year study period in Protect-Pace was insufficient to show a major clinical change in LVEF and a longer follow-up may have demonstrated a further reduction. Another study, currently ongoing, has a 3-year follow-up period. A previous study with 4-year follow-up did not show any change in LVEF although overall patient numbers were small, whereas a small randomized study over 7 years showed that RVOT pacing was associated with a lower incidence of persistent AF and less reduction in LV function.

In many previous studies, the final lead position was difficult to determine, or was often either not, or inaccurately classified. This is important, as for non-RVA pacing the final lead position may be a potential confounder to the LV response. Placement of the lead on the anterior RV wall, away from the septum, may produce a result similar to RVA pacing. Thus, any beneficial effect of septal pacing may be

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### Table 2  The final lead position as determined by the lead adjudication committee and randomization assignment

<table>
<thead>
<tr>
<th>LAC adjudication</th>
<th>Apical</th>
<th>Septal</th>
<th>Non-septal</th>
<th>Undetermined/ inconclusive</th>
<th>Not available for LAC adjudication*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization assignment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apex</td>
<td>109</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>119</td>
</tr>
<tr>
<td>High Septum</td>
<td>10</td>
<td>79</td>
<td>25</td>
<td>4</td>
<td>0</td>
<td>118</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>79</td>
<td>27</td>
<td>7</td>
<td>5</td>
<td>237</td>
</tr>
</tbody>
</table>

*Excluding subjects who withdrew before surgery or were not successfully implanted.
negated by the deleterious effects of non-septal, non-apical pacing. Placing a lead accurately at the RV septum is difficult.\textsuperscript{18,24} We attempted to maximize effective lead placement at the septum by using a steerable sheath system and clear guidance for implanters by use of a fluoroscopy-based grid system together with bi-plane imaging at the time of implant. Traditional lead technology at the time of study design was known to be unreliable in achieving accurate lead placement.\textsuperscript{18} Recent changes in lead stylet technology and design may allow more reliable septal lead placement to be obtained without the use of a steerable sheath system.\textsuperscript{31} In the Protect-Pace study, the overall success rate for septal lead placement utilizing this protocol was 66%.

Variation in the outcome of previous studies has also been influenced by significant variation in percentage of ventricular pacing. In the Protect-Pace study, the high percentage of pacing and the confirmed septal lead position in the subgroup analysis strongly support the result that RVHS pacing does not confer a benefit in protecting LVEF above that of RVA pacing, when pacing is close to continuous.

Baseline LV function is another potentially important determinant of the LV response to pacing. In a previous acute pacing study,\textsuperscript{32} RVA pacing in normal LV function produced little in the way of dysynchrony but as baseline LV function worsened, the amount of dysynchrony was greater. This would suggest that baseline LV function is important in the response to right ventricular pacing. In contrast, the Protect-Pace inclusion criteria were highly uniform in the selection of patients with preserved LV function.

In patients in whom baseline LV function is impaired, and possibly where there is ongoing pathology likely to cause future deterioration in LV function (such as ischaemia, poorly controlled systemic hypertension or diabetes), pacing outside the RVA may be desirable. It is also possible that pacing anywhere in the RV may be deleterious and it is increasingly likely that biventricular pacing will need to be considered more widely in patients with a high-degree heart block despite this being time-consuming, more expensive and associated with a higher complication rate. The Block-HF study showed a benefit for biventricular pacing in patients with an AV block and impaired baseline LV function.\textsuperscript{33} Where baseline LV function is preserved, data from the Protect-Pace study do not support a more favourable lead position compared with the apex. Our comparison did not consider biventricular pacing as a treatment arm, an obvious potential area for future study.

Study limitations

The main limitations were due to difficulty in accurately placing a lead at the RVHS and the influence of non-evaluable data. It is possible that those leads placed outside the RVHS will have confounded the overall result. However, it was felt that this is unlikely as analysis based on actual lead position produced the same result for changes in LVEF. Transthoracic echocardiography was selected as the endpoint, based on availability and the previous literature: alternative imaging approaches using three-dimensional echocardiography or cardiac magnetic resonance may be more accurate but were less available and the latter requires specific pacemaker selection. The study was planned for a 10% non-evaluable data over the 2-year follow-up period and a 10% loss due to patient death and non-compliance. As there was a 20% non-evaluable data for the primary end-point (LVEF) imputation was required to support the ITT analysis. However, data analysis based upon ITT and an ad hoc subanalysis of lead position gave the same LVEF outcome.

Conclusions

Pacing from either RVA or RVHS results in a small but statistically significant reduction in overall LV function over a 2-year period, but RVHS does not confer any protective (or detrimental) effect on LV systolic function over RVA pacing. Thus, there is no current indication to change standard pacing practice with regard to RV lead placement, as this remains a safe and effective treatment for a high-degree AV block. Other strategies (such as the extended use of CRT) may need to be examined to prevent gradual deterioration in LVEF culminating in clinical LV dysfunction and subsequent heart failure in the large, expanding and aging population of pacemaker patients.

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Conflict of interest: Since the study was closed, G.K. has received grant from the Medtronic Foundation.

Appendix

Recruiting centres

Princess Alexandra Hospital, Woolloongabba, Queensland, Australia (Dr Gerald Kaye), Royal Brisbane and Women’s Hospital, Brisbane, Australia (Dr Paul Martin), Leeds General Infirmary, Leeds, UK (Dr Chris Pepper), Colchester General Hospital, Colchester, UK (Dr Kare Tang), Christchurch Hospital, Christchurch, New Zealand (Dr Ian Crozier), Blackpool Victoria Hospital, Blackpool, UK (Dr Graham Goode), Royal Adelaide Hospital, Adelaide, Australia (Dr Glenn Ng), New Cross Hospital, Wolverhampton, UK (Dr Sanjiv Petkar), Princess Royal Hospital, Orpington, Kent, UK (Dr Ed Langford), The James Cook University Hospital, Middlesbrough, UK (Dr Nicholas John Linker), Royal Bournemouth Hospital, Bournemouth, UK (Dr Adrian Rozkovec), St Thomas Hospital, London, UK (Dr Aldo Rinaldi), University Hospital of Wales, Cardiff, UK (Dr Zaheer Yousef), Auckland City Hospital, Auckland, New Zealand (Dr Nigel Lever), The Prince Charles Hospital, Brisbane, Australia (Dr Russell Denman), Calvary Wakefield Hospital, Adelaide, Australia (Dr Glen Young), Norfolk and Norwich
References


