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Patients with long term permanent pacemakers have a high prevalence of left ventricular dysfunction

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Abstract

Introduction: Patients with right ventricular (RV) pacemakers are at increased risk of left ventricular (LV) systolic dysfunction (LVSD). We aimed to establish the prevalence, degree and associations of LVSD in patients with long term RV pacemakers listed for pulse generator replacement (PGR).

Methods: All patients listed for PGR at Leeds General Infirmary were invited to attend for an assessment during which we recorded medical history, symptomatic status, medical therapy, date and indication of first implantation, the percentage of RV pacing (%RVP) and an echocardiogram.

Results: We collected data on 491 patients. An LV ejection fraction <50% was observed in 40% of our cohort, however this was much higher (59%) in those with >80%RVP than in those with <80%RVP (22%)(p<0.0001). Multivariable analysis revealed %RVP, (but not complete heart block at baseline), serum creatinine and previous myocardial infarction to be independently related to the presence of LVSD. A model combining %RVP and previous myocardial infarction has a c-statistic of 0.74 for predicting LVSD. After a mean follow-up time of 668 days, 56 patients (12%) were dead or had been hospitalised for heart failure. In multivariable analysis, previous myocardial infarction and high %RVP were independently associated with a worse survival.

Conclusions: Patients with RV pacemakers have a high prevalence of LVSD and this is greater in those exposed to more RV pacing. Those with LVSD and high amounts of RV pacing are at higher risk of hospitalisation or death. Simple variables can identify those patients who might benefit from a more comprehensive review.

Introduction

The treatment of bradycardia by implantation of an artificial cardiac pacemaker is a routine procedure associated with extended longevity for those with atrio-ventricular (AV) block [1][2] and improved quality of life for patients with sick sinus syndrome.[3] However, long term right ventricular (RV) pacing is associated with adverse remodelling of the left ventricle,[4] which can contribute to or cause left ventricular systolic dysfunction (LVSD),[5] or overt heart failure.[6] In prospective studies of patients receiving standard RV pacemakers, subsequent hospitalisation for heart failure varies from 10% to 26%,[6][7] possibly, although not consistently,[8] related to the amount of RV pacing delivered,[6] and baseline features such as the presence of impaired left ventricular (LV) function, atrial fibrillation and older age at implant [7][9] and paced QRS.[10] In a cross-sectional study in patients attending a pacemaker follow-up clinic we have previously demonstrated a prevalence of heart failure symptoms with LVSD of 27%.[11]

One third of all pacemaker procedures are to replace an expired existing pacemaker generator, and this proportion is increasing.[12] These patients might be at even higher risk for underlying LVSD and heart failure in view of their older age, longer duration of RV pacing, and underlying cardiac disease. The time of a pulse generator replacement (PGR) presents an opportunity to review symptoms, LV function, medical therapy and device prescription, but this is rarely done.[13] We therefore undertook this pragmatic prospective observational study to assess the prevalence and associations of LV

dysfunction in patients with long-term RV pacemakers booked for an elective generator replacement.

Methods

All individuals listed for elective pacemaker generator replacement at Leeds General Infirmary between 1st March 2008 and 1st December 2011 were invited to attend the cardiology department at least one week prior to the procedure. We did not enrol patients with implantable cardioverter defibrillators (ICDs) or patients with cardiac resynchronisation devices and we also excluded patients with congenital structural heart disease (but not those with congenital heart block). A series of variables including height, weight, blood pressure, symptomatic status (New York Heart Association category), medical therapy (including bisoprolol-equivalent beta-blocker dose [14]), past medical and cardiac history, the date of first implantation and indication and the number of subsequent pacemaker generator replacements were recorded. The implant indication was confirmed by reviewing the baseline electrocardiograph tracings and the medical records. The pacemaker was interrogated to document programming and the percentage of right atrial and RV paced (%VP) beats over the preceding twelve months. Previous data have suggested an increased risk of hospitalisation for heart failure with >80% VP (for VVI pacing) and 40% for DDDR pacing.[6]

A 12-lead electrocardiogram was recorded in each individual to measure QRS duration during a paced beat (achieved by shortening the AV delays in those with preserved conduction). Each patient underwent a full echocardiographic

examination (Vivid 9, Vingmed, USA). We used an LVEF of <50% measured by the Simpson's biplane methods averaged from three consecutive beats as our cut-off for LVSD.[15] In those without important neuromuscular, skeletal, pulmonary, and other conditions precluding exercise testing, formal symptom-limited treadmill-based peak cardiopulmonary exercise testing was carried out to establish peak oxygen consumption (Medgraphics, USA), and heart rate and blood pressure responses to exercise. A single blood draw was performed either at this visit or immediately prior to the procedure to measure renal function and blood count.

For hospitalisation and mortality we chose a censor date of 31st December 2011 and all patients who attended the assessment were included in the final analysis. Morbid status and hospitalisation were established from written and electronic records and communications with local general practitioners and the diagnosis at admission or cause of death recorded.

Data analysis was undertaken using SPSS version 18. Relationships between variables were explored initially using simple regression and subsequently by multiple regression. Differences between groups were explored using Student's t-test and a Cox proportional hazard model was used to compute the hazard ratio and corresponding 95% confidence intervals for subsequent mortality or hospitalisation for heart failure. Normally distributed continuous data are presented as means (95% confidence intervals (CI)). For continuous variables without normal distribution, identified by the Shapiro-Wilk test, we have presented median and interquartile range (IQR). We also used %VP

transformed to a categorical variable and analysed with an interaction test and ANOVA to identify at which category of VP there was a reduced LVEF. Predictive model calibration and discrimination was assessed using Hosmer-Lemeshow and receiver operating characteristic (ROC) curve assessment, respectively. The study was approved by the Leeds West Research Ethics Committee (08/H1307/12).

Results

Of the 508 patients undergoing pacemaker generator replacement in the study period, we collected a complete dataset on 491 (97%). Patients not assessed (or in whom data-points were missing) were not different in terms of age, pacemaker variables or co-morbidities. Table 1 shows demographic and basic pacemaker data. Cardiovascular co-morbidities (43% had overt ischæmic heart disease, 27% atrial fibrillation and 13% diabetes mellitus) and concurrent cardiovascular medical therapies were common.

DEVICE PRESCRIPTION AND PROGRAMMING

Table 2 summarises the nature of the devices and their programming. All patients' right ventricular leads were in the apical position. Patients in sinus rhythm were more likely to have a dual chamber device *in situ* than patients in atrial fibrillation (93 v 49%; p<0.0001), but there was no age difference between those with and without dual chamber devices. The most common indication for pacemaker implantation was sinus node disease (57%), with 42% having an indication of atrio-ventricular conduction delay (AV-delay) including 27% of the total with third degree block (complete heart block

(CHB)) at baseline (table 1). Patients receiving a pacemaker for CHB at baseline had a higher %VP at the time of PGR (85 (79-91) v 50 (46-54)%; p<0.0001) than those without CHB at baseline, and although 78% of those with CHB at baseline had >80%VP at PGR, 12% had less than 40%VP at follow-up. Furthermore, 37% of patients implanted for AV block but not CHB at baseline were receiving >80%VP at the time of PGR.

There was a weak correlation between age and %VP, (r=0.1; p=0.014) and patients with >80%VP were older. There was no correlation between the presence of cardiovascular co-morbidities (myocardial infarction, percutaneous coronary angioplasty, hypertension, or cardiac surgery), seen in 50% of the population, and the %VP. On the other hand, there was a relationship between %VP and renal function, (r=0.20; p=0.0077) and furosemide requirements (r=0.2; p<0.02), and patients with >80%VP at PGR had significantly worse renal function (eGFR 53 (49-57) v 60 (56-64); p=0.01).

Rate response mode was more commonly activated in patients with atrial fibrillation (66 v 41%; p<0.0001), and was associated with a higher %VP in single chamber (but not in dual chamber) devices (%VP 78 (70-86) v 59 (45-73)%; p=0.009). As a consequence patients with single chamber devices experienced a higher %VP than those with dual chamber devices (71 (67-75) v 53 (50-56)%; p=0.0002).

ECHOCARDIOGRAPHIC AND CARDIOPULMONARY EXERCISE RESULTS

Table 2 shows the results of non-invasive testing in patients attending for PGR. The mean and median LVEF were both 50% and the range was 12-74%. An interaction plot demonstrated that mean LVEF was only significantly lower in patients with %VP>80% so we used this as our cut off for further analyses. The prevalence of LV dysfunction (LVEF<50%) was 40% in our cohort, but this was significantly higher in those with i) >80%VP (59%) compared with <80%VP (22%)(p<0.0001) and ii) those with cardiovascular co-morbidities (figure 1). Patients with LV systolic dysfunction were more likely to be taking β-blockers (79 v 47%; p<0.0001) and ACE-inhibitors (or angiotensin receptor blockers)(83 v 63%; p<0.0001)), although, daily doses were suboptimal (mean bisoprolol equivalent 4.5 (0.5)mg, with only 10% on the maximal bisoprolol-equivalent dose) and only 16% on an aldosterone receptor antagonist.

Patients with CHB at baseline had worse mean LV function at PGR than those without baseline CHB (LVEF 46 (44-48) v 52 (50-54)%; p=0.0008, X^2 for LVEF<50%=7.6; p=0.006). However, the difference in LVEF between those with and without >80%VP at PGR were more significant (LVEF 55 (53-57) v 46 (44-48)% and X^2 for LVEF<50%=48; p<0.0001).

Simple regression suggested relationships between LVEF and age (r=0.15 p=0.006), %VP at PGR (r=0.40; p<0.0001), serum creatinine (r=0.26; p<0.0001), paced QRS width (r=0.41; p=0.0003), and furosemide dose (r=0.32; p=0.0001). In a multivariable model only %VP at PGR, serum

creatinine and previous myocardial infarction remained significant (table 3). These three variables gave a c-statistic of 0.79 (0.72-0.86) and a negative predictive value of 89% with a 20% risk cut-off for identifying the presence of LVEF<50%. Figure 2 shows the ROC curve for predicting LVEF <50% using two variables easily available at every review: %VP at PGR and a history of previous myocardial infarction. Using these two variables alone, our model has a negative predictive value of 90%, a positive predictive value of 51%, with a c-statistic of 0.74 (0.68-0.81)(Hosmer Lemeshow p-value of 0.95).

Peak oxygen consumption (pVO_2) was available in 159 (33%) patients. Patients with pacemakers have significantly limited exercise capacity, which is lowest in those with the highest amount of ventricular pacing (>80%VP) (pVO_2 15 (13-17) v 20 (18-22) ml/kg/min; p=0.0001). In multiple regression analysis, peak oxygen consumption was related to age, renal function and furosemide requirement rather than any marker of pacemaker activity.

OUTCOME DATA

We included all patients seen in our correlative analyses, but excluded 25 patients enrolled into a randomised study of upgrade to cardiac resynchronisation therapy in our prospective analysis of outcome. This left a population of 466 with the same mean baseline characteristics as the original population. After a mean follow-up time of 668 (19) days, 56 patients (12%) were dead (n=34) or had been hospitalised (n=22) for heart failure. Univariable predictors of mortality or hospitalisation for heart failure are shown in Table 4. On multivariable analysis, previous myocardial infarction and high

%VP were independently associated with a worse survival. The Kaplan Meier curves for patients with and without LVEF <50% and with and without %VP>80% are shown in Figure 3.

Discussion

The present data, the first to explore systematically a contemporary cohort of patients undergoing standard pacemaker generator replacement, demonstrate a high prevalence of LV dysfunction and cardiovascular co-morbidity and a mortality rate only modestly lower than that of heart failure patients of similar age.[14] The presence of LV dysfunction is independently related to the amount of RV pacing and, particularly when combined with a high percentage of ventricular pacing, LV dysfunction portends an adverse prognosis.

In retrospective analyses [16][17] and one prospective study [9] of patients receiving new pacemakers, the most consistent feature predicting outcome was LVSD at baseline although age, coronary artery disease, co-morbidities (chronic airways disease and diabetes mellitus), paced QRS (for subsequent hospitalisation),[18] and atrio-ventricular block are also associated with a worse outcome. In our cohort pacing mode or indication was not relevant once %VP and the presence of LV dysfunction had been taken into account.

We have been able to construct a model based upon simple pacemaker-related and clinical variables (>80%VP and previous myocardial infarction) that has a negative predictive value of 90% for LVSD and a c-statistic of 0.74

(0.68-0.81). This would form an easy way to select patients who might benefit from a more extensive review, although whether such a review and the effects of interventions undertaken upon identifying LVSD impacts subsequent outcomes in this population requires further work.

Aetiology of RV pacing-associated left ventricular dysfunction

RV pacing induces ventricular dyssynchrony,[19] similar to that seen in intrinsic left bundle branch block (LBBB),[20][21] which leads to altered regional blood flow and wall stress, increased cardiac sympathetic activity,[4] and left ventricular dysfunction directly related to the duration of ventricular pacing.[22] Hence, RV apical pacing could either induce LV dysfunction or accentuate pre-existing latent LV dysfunction. Which features identify patients at high risk of future LV dysfunction is unclear.

Management of RV-pacing associated LV dysfunction

Studies exploring the medical management of patients with pacemakers and LV dysfunction are rare,[23] and although patients with pacemakers and heart failure were not excluded from all trials of medical therapy, subgroup analysis of the paced population was not undertaken in any of the large studies. For example whether, in a patient with LVSD and a pacemaker, the benefit of high-dose β-blockers compensates for the adverse effects of ventricular pacing is unknown.

Since RV pacing contributes to poorer outcomes,[24] reducing this might improve LV function or prevent further deterioration. Although >80%VP in VVI

mode and >40%VP in DDD mode are associated with an increased rate of hospitalisation for heart failure,[6] it is unknown whether there is a target of %VP below which the risk of subsequent or deteriorating LVSD is low and whether this is different in patients with established LVSD. Reducing RV pacing in patients with existing RV pacemakers can improve LV systolic dysfunction [25] and reduce the incidence of atrial arrhythmias.[26][27][28][29][30]

Reprogramming is not an option in heart failure patients with standard pacemakers with complete heart block or a slow response to atrial fibrillation. These patients frequently receive an upgrade procedure to cardiac resynchronisation therapy (CRT). It is thought that this leads to similar improvements in clinical variables and measures of LV function as with de-novo CRT implants.[20][31][32][33]

Upgrading to CRT at the time of PGR those patients with a high percentage of pacing and LV systolic dysfunction (LVEF<50%) but few symptoms improves quality of life, LV function, and exercise capacity while reducing NT-pro-B-type natriuretic peptide, and might reduce heart failure events,[34] but larger studies are required to provide data on hard endpoints. A registry of successful upgrades, although useful, is not enough.[35]

Preventing RV pacing-associated LV dysfunction

Our findings also have implications for the use of 'prophylactic' CRT in patients requiring rate support. Complete heart block (CHB) at baseline only

modestly predicts high %VP at long term follow-up, yet 65% of patients with AV node disease but without CHB at implant go on to >80%VP. Hence CHB at baseline represents only 80% of those eventually requiring >80%VP.[36] Also, despite high %VP, some patients in our cohort seem resistant to the adverse effects of RV apical pacing. Since CRT at baseline does not universally prevent a deterioration in LV function,[37] the benefits of prophylactic CRT *versus* RV pacing in an unselected population may be marginal,[38] requiring careful risk stratification to identify patients in whom CRT for bradycardia is cost- and clinically-effective. The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) study,[39] set out to determine whether CRT for bradycardia is better than standard RV pacing in patients with mild LVSD (EF<50%). Patients receiving biventricular pacing had lower rates of death from any cause, urgent heart failure care or increase in left ventricular end systolic volume index (LVESI) of >15% from baseline. However, the study included patients with an existing CRT indication (30% had LVEF<35% and mean QRS duration was 125ms), for whom 'standard care' meant high rates of RV pacing with the additional upfront higher risk of a CRT pacemaker implantation. Some patients may have experienced more adverse events than would be expected with a dual chamber pacemaker programmed to avoid pacing. The lack of a control arm (all patients received a CRT device with the LV lead deactivated in those randomised to standard RV pacing) means that cost-benefit and cost-utility analyses cannot be done.[40] One large randomised study looking at the effects on morbidity and mortality of CRT versus RV pacemaker systems in patients with a bradycardia has

completed recruitment.[41] Although there is growing enthusiasm for right ventricular septal pacing there are as yet no hard endpoint data to support widespread adoption of this strategy.[42][36]

Limitations

The present data do not include patients with new implants that did not survive to generator replacement, and therefore represent a selected population. However, even these 'survivors' have an appreciable subsequent morbidity and mortality so a generator replacement procedure might be an appropriate time point to review medical and device therapy.

Merely diagnosing the presence of LVSD might have led to changes in therapy and programming and therefore outcomes. A future study might benefit from randomisation to provide a cohort of 'usual care' patients who do not undergo echocardiography.

We also excluded from our analysis of survival, the 25 patients with LVSD and high %VP that consented to be enrolled into a study of cardiac resynchronisation versus standard generator replacement. This might have served to reduce the degree of morbidity and mortality associated with high amounts of RV pacing and LVSD in our cohort.

By demonstrating a dose-response relationship between the amount of ventricular pacing and the degree of LV dysfunction, we have fulfilled one of the requirements for causality.[43] We appreciate that we do not have

echocardiographic data on our patients at the time of their first pacemaker implantation. Hence we cannot comment on whether, and in what circumstances, RV pacing induces LV dysfunction. Our stated aim was not however, to identify features at baseline that predict future LVSD, rather our aim was to provide a platform with which to stratify risk in order to identify those patients with existing pacemakers in whom further investigation might be of most benefit.

Our dataset and the analysis, although prospectively collected cannot account for unknown confounders and our findings along with our risk model require validation and refining in future larger internal and external cohorts.

Conclusions

Patients with RV pacemaker systems listed for elective generator replacement have a high prevalence of left ventricular systolic dysfunction strongly correlated with the amount of RV pacing to which they are exposed. Those with left ventricular systolic dysfunction and high amounts of RV pacing are at high risk of subsequent mortality. Simple variables (the presence of >80% VP and a previous myocardial infarction) can identify patients who might benefit from a more comprehensive review including echocardiography around the time of generator replacement but whether there are benefits of optimising medical and device therapy in pacemaker patients with cardiac dysfunction requires further investigation.

Disclosures and acknowledgements

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