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Risk of heart failure- and cardiac death gradually increases with more right ventricular pacing☆,☆☆

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ABSTRACT

Background: Right ventricular pacing (RVP) is associated with an increased risk of heart failure (HF) events. However, the extent and shape of this association is hardly assessed.
Objective: We quantified whether the undesired effects of RVP are confirmed in an unselected population of first bradycardia pacemaker recipients. Furthermore, we studied the shape of the association between RVP and HF death and cardiac death.
Methods: Cumulative percentage RVP (%RVP) was measured in 1395 patients. Using multivariable Cox regression analysis with %RVP as time-dependant co-variate we evaluated the association between %RVP and HF- and cardiac death, both unadjusted and adjusted for confounders, including age, gender, pacemaker-indication, cardiac disease, HF at baseline, diabetes, hypertension, atrio-ventricular synchrony, usage of beta-blocking drugs, anti-arrhythmic medication, HF medication, and prior atrial fibrillation/flutter. Non-linear associations were evaluated with restricted cubic splines.
Results: During a mean follow-up of 5.8 (SD 1.1) years 104 HF deaths and 144 cardiac deaths were observed. %RVP was significantly associated with HF- and cardiac death in both unadjusted ($p < 0.001$ and $p < 0.001$, respectively) and adjusted analyses ($p = 0.046$ and $p = 0.009$, respectively). Our results show a linear association between %RVP and HF- and cardiac death. We observed a constant increase of 8% risk of HF death per 10% increase in RVP. A model incorporating various non-linear transformations of %RVP using restrictive cubic splines showed no improved model fit over linear associations.
Conclusion: This long-term, prospective study observed a significant, though linear association between %RVP and risk of HF death and/or cardiac death in unselected bradycardia pacing recipients.

1. Introduction

Right ventricular pacing (RVP) causes left ventricular mechanical dyssynchrony by inducing electrical interventricular and intraventricular dyssynchrony [1]. The abnormal ventricular electrical activation can eventually result in long-term adverse effects of the cellular structure and ventricular geometry. The ventricular remodeling can lead to systolic and diastolic dysfunction, mitral regurgitation and increased left atrial diameter that contribute to impaired hemodynamic performance of the left ventricle (LV) [2–4]. Subsequently, clinical studies showed an increased risk of heart failure (HF) [5,6], a reduction in LV function [7], and an increased risk of HF death in patients receiving frequent RVP [5,6,8]. Following these observations, efforts have been undertaken to prevent unnecessary RVP [9–12], and to explore alternative pacing sites to prevent detrimental long-term effects of chronic RVP [10,13–15].

At present, insight in the relation of event risk to percentage RVP (%RVP) is lacking. While the hypothesis was derived from ICD recipients, information about the effect of %RVP in the most applicable patient population, namely the bradycardia pacemaker (PM) recipient, remains very scarce. Only few studies addressed this issue in PM patients and showed conflicting results [16–18]. While some studies suggest a clear association between RVP and HF [19], others fail to show any effect [16–18,20,21]. Furthermore, the shape of the relation between %RVP and HF events is still unclear: concepts vary from a linear association to non-linear association, to thresholds of varying risk for ranges of %RVP [19,22]. This study was performed to provide insight in the shape of this association, which would be valuable to direct preventive measures regarding pacing induced HF.

The Dutch FOLLOWPACE study was designed to evaluate outcomes in a large nationwide, contemporary, unselected prospective cohort of patients receiving a first PM for conventional bradycardia indications.

Abbreviations: PM, pacemaker; HF, heart failure; RVP, right ventricular pacing; %RVP, percentage right ventricular pacing.

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The design of FOLLOWPACE with detailed recording of %RVP during long-term observation of daily practice without study prescribed interventions influencing %RVP, provided the unique opportunity to examine whether the observed %RVP is associated with HF death, cardiac death and/or all-cause death, and to investigate the shape of its association across the range of RVP values.

2. Methods

2.1. Patients

The nationwide FOLLOWPACE study is a prospective multicentre cohort study conducted in 23 PM centers in the Netherlands. The design of the FOLLOWPACE study has been published previously [23]. In brief, consecutive patients aged 18 years or older who received a first PM for a conventional reason for chronic pacing [24] were eligible. Patients were not eligible if they were taking any investigational drug, had a non-approved or investigational PM or a resynchronisation PM implanted. In addition, patients with a life expectancy of <1 year at time of implantation were excluded. For the present analysis patients who died within 3 months after implantation were excluded to allow for collecting of %RVP [22].

At time of implantation (baseline), patient demographics, medical history, medication use, and PM and procedural data were systematically recorded according to a pre-specified protocol. Coexistent cardiac disease was defined as a history of myocardial infarction, prior cardiac surgery (coronary artery bypass grafting or valve surgery), prior coronary angioplasty, and/or valve disease documented before PM implantation. All patients provided written informed consent before PM implantation. This study complies with the Declaration of Helsinki and the protocol for the study was approved by the Ethical Commission of the University Medical Center Utrecht. Inclusion took place between January 2003 and November 2007.

2.2. Percentage right ventricular pacing

After implantation, the frequency and intervals of subsequent follow-up visits and actions performed during these visits in terms of device reprogramming or medication adjustments were at the discretion of the medical professional in charge following current clinical standards. Study participation dictated no special interventions, but only documented local PM practice. At each follow-up visit, the percentage right ventricular pacing (%RVP) was determined from stored PM diagnostic data and calculated as the number of ventricular paced beats over the total number of beats for the life of the device. When %RVP was not recorded at a particular visit, the next available measurement was considered representative and included in the analysis. Because the %RVP was not known at time of death, the last recorded %RVP was carried forward until time of death. To reduce potential bias only patients with >33% of %RVP measurements available, were included in the analysis.

2.3. Outcome measurement

Follow-up was completed on 1 November 2010. Each patient was followed for at least 3.3 years after PM implantation. Vital status data were available for all patients at end of follow-up. Cause of death was classified as cardiac or non-cardiac, and cardiac deaths were further classified as either death due to myocardial infarction, arrhythmic death, HF death, PM-related death, after resuscitation for unknown cause, or unknown cardiac cause of death. The primary outcome of interest was HF death, defined as death occurring within the course of or in the immediate period after hospitalization or treatment of worsening congestive HF, in the absence of the suggestion of cardiac ischemia. Secondary outcomes were cardiac death and all-cause mortality. Classification of causes of death took place by an independent committee unaware of %RVP, after review and discussion of hospital files. The general practitioner or medical service in case of nursing homes was contacted to inquire about vital status when no documentation of medical contact was found during 6 consecutive months.

2.4. Statistical analysis

We used Cox proportional hazard models with time to HF death, cardiac death or all cause death, respectively, as the dependent variable, and %RVP as time-dependent co-variate. The model thus accounts for different levels of RVP over varying timeframes during the life of each included patient. In each step we extended the model, making it more detailed, in order to more accurately describe this relationship. The added descriptive value of the more complex model was tested using likelihood ratio-test [25].

First, linear associations were assessed, both adjusted and unadjusted. As the aim of this study was to test for an association between %RVP and our endpoints, potential confounders for HF death were included in the multivariable model: age, gender, PM indication, cardiac disease, known HF, diabetes, hypertension, prior atrial fibrillation/flutter, atrioventricular synchrony, anti-arrhythmic medication, medication for HF (digoxin, angiotensin-converting enzyme inhibitors, or angiotensin receptor blocker), and the use of beta-blockers as time dependent covariate.

Non-linear associations were studied by incorporating restrictive cubic splines to both the adjusted and unadjusted Cox models [26]. Adding these non-linear components for RVP allowed modeling a different hazard ratio (HR) for different ranges of %RVP. For instance, adding restrictive cubic splines with 2 knots at 25% and 75% pacing, enables modeling different HR's for the ranges 0–25%, 25–75% and 75–100% pacing. We also investigated in our data the non-linear association previously observed by Sweeney et al. [19], with restricted cubic spline knots at the level of 40% and 80% pacing.

The statistical power for detecting associations in time-to-event analysis is determined by the number of events [25]. For this analysis the number of events was relatively low compared to the number of coefficients (hazard ratios) to be estimated. A slightly higher significance level (p-value <0.10) was therefore used [27].

Statistical analyses were performed with the rms package in R (version 2.15.0) [26].

3. Results

3.1. Patients

FOLLOWPACE included a total of 1517 patients. For the present analysis 43 patients who died in the first 3 months after implantation were excluded. After excluding 23 patients with <33% of possible %RVP measurements available, and 56 patients with a single measurement of %RVP, a total of 1395 (92%) patients were included in the analysis (Table 1). Median age at the moment of first implant of the included patients was 76 year and 785 (56.3%) were male patients (Table 1). Indication for PM implantation was atrioventricular conduction disturbances in 571 (40.9%), sick sinus syndrome (SSS) or bradyarrhythmias in 504 (36.1%), atrial fibrillation with slow ventricular response in 251 (18.0%) and other indications as hypersensitive carotid sinus syndrome, or intraventricular conduction disorders in 69 patients (4.9%). Most implanted PMs were dual-chamber devices (74.1%). All right ventricular leads were positioned at the right ventricular apex.

During follow-up a total of 13,353 technical device check-ups were performed. The median number of follow-up visits per patient was 9 (interquartile range 7–12), and in a median of 71% (interquartile range 54–86%) of these visits the %RVP was measured.

During a mean follow-up of 5.8 (SD 1.1) years a total of 440 patients died. Of these, 104 patients died of HF and 144 of cardiac death (Table 2). Survival free from HF death at 6 years was 77% and 93% for