Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function

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BACKGROUND Right ventricular (RV) pacing may worsen left ventricular cardiomyopathy in patients with reduced left ventricular ejection fraction (LVEF) and advanced atrioventricular block.

OBJECTIVE The objectives of this study were to calculate incidence and identify predictors of RV pacing-induced cardiomyopathy (PICM) in complete heart block (CHB) with preserved LVEF and to describe outcomes of subsequent cardiac resynchronization therapy (CRT) upgrade.

METHODS An analysis of consecutive patients receiving permanent pacemaker (PPM) from 2000 to 2014 for CHB with LVEF >50% was performed. PICM was defined as CRT upgrade or post-PPM LVEF ≤40%. PICM association was determined via multivariable regression analysis. CRT response was defined by LVEF increase ≥10% or left ventricular end-systolic volume decrease ≥15%.

RESULTS Of the 823 study patients, 101 (12.3%) developed PICM over the mean follow-up of 4.3 ± 3.9 years, with post-PPM LVEF being 33.7% ± 7.4% in patients with PICM vs 57.6% ± 6.1% in patients without PICM ($P < .001$). In multivariable analysis, lower pre-PPM LVEF (hazard ratio [HR] 1.047 per 1% LVEF decrease; 95% confidence interval [CI] 1.002–1.087; $P = .042$) and RV pacing % both as a continuous (HR 1.011 per 1% RV pacing; 95% CI 1.002–1.02; $P = .021$) and as a categorical (<20% or ≥20% RV pacing) (HR 6.76; 95% CI 2.08–22.0; $P = .002$) variable were independently associated with PICM. Only 29 patients with PICM (28.7%) received CRT upgrade despite an 84% responder rate (LVEF increase 18.5% ± 8.1% and left ventricular end-systolic volume decrease 45.1% ± 15.0% in responders). CRT upgrade was associated with greater post-PPM LVEF decrease, lower post-PPM LVEF, and post-PPM LVEF ≤35% ($P = .006$, $P = .004$, and $P = .004$, respectively).

CONCLUSION PICM is not uncommon in patients receiving PPM for CHB with preserved LVEF and is strongly associated with RV pacing burden >20%. CRT response rate is high in PICM, but is perhaps underutilized.

KEYWORDS Atrioventricular block; Cardiac resynchronization therapy; Cardiomyopathy; Complete heart block; Ejection fraction; Heart failure; Incidence; Pacing; Pacing-induced cardiomyopathy; Predictors

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Introduction

Right ventricular (RV) pacing is known to produce electric and mechanical dyssynchrony by triggering the right ventricle to contract before the left ventricle (interventricular dyssynchrony) and the septum to contract before the lateral walls (intraventricular dyssynchrony).[1] Historically, adverse clinical events were first attributed to RV pacing in patients with sinus node dysfunction, with higher rates of congestive heart failure (CHF), atrial fibrillation, and chamber dilation observed as compared to AAI pacing.[2,3] Thereafter, increased CHF and mortality were seen with DDDR 70 vs VVI 40 pacing in the Dual Chamber and VVI Implantable

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Defibrillator (DAVID) trial,[4] a different patient population enrolling patients with left ventricular (LV) ejection fraction (LVEF) ≤40% receiving implantable cardioverter-defibrillators (ICDs) without concurrent indication for bradycardia pacing. Post hoc analyses of both the DAVID and MOST[5] trials,[6,7] independently identified a threshold of >40% RV pacing in DDDR mode as a predictor of CHF hospitalization. When accompanied by a decrease in LV systolic function post-RV pacing without an alternative identifiable trigger, this condition is termed *pacing-induced cardiomyopathy* (PICM).

In an effort to prevent PICM in patients with preexisting LV systolic dysfunction, the BLOCK-HF trial[8] prospectively randomized patients with high-degree atrioventricular (AV) block, preexisting CHF, and LVEF ≤50% to standard permanent pacemaker (PPM)/ICD vs biventricular PPM/ICD, referred to as cardiac resynchronization therapy (CRT). Over a mean follow-up of 3 years, a 10% higher absolute rate of CHF hospitalization and/or 15% increase in LV end-systolic volume (LVESV) index was observed in the standard RV pacing cohort. Although not yet formally integrated into current device guidelines,[9] up-front implantation of CRT in patients with advanced AV block and LVEF ≤50% has been approved by the US Food and Drug Administration as acceptable in current clinical practice.[10]

While the risk of PICM is well established in patients with prepacing LV systolic dysfunction, the patterns of PICM warranting subsequent upgrade to CRT in patients with preserved LVEF are less certain. The PACE trial[11] prospectively randomized 177 patients with advanced AV block and normal prepacing LVEF (≥45%) to CRT vs standard PPM. At 1-year follow-up, the mean LVEF of 55% was 7% lower in the RV pacing group with 8 patients (9%) experiencing LVEF decrease to <45%. In a smaller (n = 26) study by Dreger et al[12] with a mean follow-up duration of ~25 years, the incidence of PICM was 15% (n = 4) with a mean LVEF decrease of 20%. In a larger (n = 304) descriptive cohort study by Zhang et al[13] requiring >90% RV pacing in patients with advanced AV block and no history of CHF, new clinical CHF was observed in 26% patients.

In this study, we analyzed consecutive data from patients undergoing PPM implantation for complete heart block (CHB) with preserved preimplant ejection fraction (≥50%) at a large, quaternary care, US academic center. The study objective was to define the incidence and predictors of PICM in this patient population, in addition to the clinical outcomes associated with subsequent CRT upgrade.

Methods

Study population

After institutional review board approval, data query was performed to identify consecutive adult patients undergoing PPM implantation for CHB at Cleveland Clinic (Cleveland, OH) from 2000 to 2014. A second data query was then performed to censor patients based on the following inclusion criteria: LVEF >50% on an echocardiogram ≤6 months pre-PPM implant. Patients were excluded if (1) PPM was a reimplant, generator change, or CRT; (2) echocardiograms <6 months were discordant with respect to LVEF >50%; and (3) lack of follow-up post-PPM.

PICM

PICM was defined as subsequent CRT upgrade or post-PPM LVEF decrease to ≤40% via echocardiography. Time to PICM was calculated from the date of PPM implant to the date of either CRT upgrade or LVEF decrease, whichever occurred first. The post-PPM LVEF threshold of ≤40% was carefully chosen to account for inherent error in LVEF estimates by echocardiography (±5% at the study site) and to maximize certainty that reported decreases in LVEF post-PPM represented true incident systolic dysfunction.

Clinical data and measurements

Electronic medical record chart review was performed for all patients. Collected clinical data included patient demographic characteristics; pre-PPM medical history, electrocardiographic, and echocardiographic findings; PPM indications; PPM procedural outcomes/settings; and post-PPM follow-up device diagnostics and echocardiographic findings. Intrinsic and paced QRS durations were recorded, with intrinsic QRS defined as the width of the escape rhythm or, if not available, the width of the conducted, nonpaced ventricular rhythm chronologically closest to PPM implantation. QRS morphology was classified as left or right bundle branch block, intraventricular conduction delay, or narrow QRS according to standard consensus criteria.[14] Ventricular lead placement was classified as apical or nonapical according to the location reported in the PPM postprocedure note and was subsequently confirmed radiographically as available. PPM settings (mode, rate adaptive, rate) were recorded both at implant and at the end of follow-up. RV pacing % was recorded at the end of follow-up, censored to an earlier date if the primary outcome was reached via either CRT upgrade or LVEF decrease to ≤40%.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as percentages. Student *t* and Pearson χ^2 tests were used to compare continuous and categorical variables, respectively. Univariable analysis was performed on collected clinical data stratified by patients with and without PICM. Clinical data categories satisfying an a priori threshold of $P < .1$ were retained for multivariable logistic regression analysis. Those categories retaining $P < .05$ in multivariable modeling were considered statistically significant. Kaplan-Meier analysis was performed and curves were constructed demonstrating survival without PICM for both the entire cohort and the cohort stratified by RV pacing %. Analyses were performed using SPSS software Version 18, July 30, 2009 (SPSS Inc., Chicago, IL).