Incidence and Time Course for Developing Heart Failure With High-Burden Right Ventricular Pacing

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Background—Although right ventricular pacing can contribute to cardiomyopathy, the impact of complete atrioventricular block (cAVB) on heart failure (HF) development in pacemaker patients has not been well characterized. We evaluated the incidence and time course for developing HF after pacemaker implantation for cAVB.

Methods and Results—A MarketScan database identified patients undergoing dual-chamber pacemaker implantation from 2008 to 2014. Patients with cAVB were identified by an atrioventricular node ablation or diagnosis of third-degree AVB. Patients with ≥1 year of continuous MarketScan enrollment before and after implant and without a previous diagnosis of HF were dichotomized into those with cAVB and without AVB. The primary end point was new HF assessed over acute (0–6 months) and chronic (6 months to 4 years) phases post–pacemaker implantation. The cohort included 6994 cAVB patients and 14208 patients without AVB, followed for 2.35 years (interquartile range, 1.62–3.39 years). After adjustment for baseline covariates, patients with cAVB experienced an increased risk of new-onset HF in the acute phase (hazard ratio, 1.62; 95% confidence interval, 1.48–1.79; P<0.001). Although the risk of HF remained elevated among those with cAVB in the chronic phase, the effect was attenuated (hazard ratio, 1.16; 95% confidence interval, 1.08–1.25; P<0.001). After pacemaker implantation, younger patients (≤55 years of age) and those with an antecedent history of atrial fibrillation experienced the highest risk of HF associated with cAVB.

Conclusions—Patients with a diagnosis of cAVB, and thus presumed to have a higher burden of right ventricular pacing, experienced an increased risk of new-onset HF after pacemaker implantation compared with those without AVB. Better tools are needed to identify patients at high risk of developing HF in the setting of right ventricular pacing and to determine whether these patients benefit from upfront biventricular pacing.

(High-burden right ventricular (RV) pacing has been associated with the development of cardiomyopathy and heart failure (HF) symptoms. Several pathophysiological mechanisms have been implicated in the development of pacing-induced HF,1–3 all of which likely stem from abnormal electrical and mechanical activation produced by RV pacing. Different definitions have been used for diagnosing pacing-induced cardiomyopathy (PICM), some of which depend on structural changes such as drop in left ventricular ejection fraction (LVEF) or increase in ventricular volumes, and others that use clinical end points such as HF events and functional capacity. Although individuals with already compromised systolic function seem to be most susceptible to the detrimental effects of RV pacing,4,5 PICM has also been demonstrated among those with normal systolic function at baseline.7,8 Even in the absence of a drop in LVEF, RV pacing may lead to symptoms of HF caused by elevation of cardiac filling pressures, functional mitral regurgitation, decreased cardiac output, and altered ventricular compliance.3,10 A few studies have looked at the incidence of HF events (primarily HF hospitalization) as a function of RV pacing burden among individuals with normal baseline LVEF, but most of these studies have been relatively small and, therefore, unable to clearly define the time course with which HF develops in the setting of RV pacing.7–9,11,12

In this large retrospective study using real-world data, we sought to characterize the incidence and time course of new-onset HF in the setting of atrioventricular disease and anticipated high-burden RV pacing. We also investigated the effect of baseline demographics and comorbidities on HF development after pacemaker implantation.

Methods

Data Source

Data used for this retrospective, observational cohort study were derived from the Truven Health MarketScan Commercial Claims and

Received January 10, 2017; accepted May 5, 2017.

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Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org

DOI: 10.1161/CIRCOUTCOMES.117.003564

Key Words: atrial fibrillation ▪ atrioventricular block ▪ cardiomyopathy ▪ heart failure ▪ incidence
WHAT IS KNOWN

• High-burden RV pacing has been associated with the development of cardiomyopathy and HF symptoms.
• The incidence, time course, and risk factors for developing pacing-induced HF have not been well characterized.

WHAT THE STUDY ADDS

• Individuals with a diagnosis of cAVB, who were presumed to have a high burden of RV pacing, had a significantly higher incidence of new-onset HF in both the acute (0–6 months) and chronic (6 months to 4 years) phases after pacemaker implantation compared with those without a diagnosis of AVB.
• Younger individuals (≤55 years old) and those with a history of AF experienced the highest risk of HF associated with high-burden RV pacing.

Medicare Supplemental databases from 2008 to 2014. The Truven databases capture paid and adjudicated billing claims data from inpatient hospital encounters, outpatient physician office visits, and pharmacy data for privately insured and Medicare Supplemental patients throughout the United States. The nationally representative databases include records from >170 million enrollees since 1995 and have supported publications on outcomes of patients undergoing cardiac procedures and implantable electronic devices.14-16 This study was a retrospective analysis of a deidentified database and, thus, was exempt from Institutional Review Board review under 45 CFR 46.101(b)(4).

Study Population

Patients were selected for study inclusion if they were implanted with a de novo dual-chamber pacemaker (Current Procedural Terminology code 33208 and Healthcare Common Procedure Coding System codes C1785 and C2619) from any manufacturer between April 1, 2008, and March 31, 2014. Patients with a left ventricular lead placed (Current Procedural Terminology codes 33224 or 33225) at the time of pacemaker implantation were excluded. De novo implants were identified as pacemaker patients without a previous device implantation and without a remote or in-office pacemaker follow-up visit in the 1 year before implantation. An enrollment indicator confirmed active inclusion in the MarketScan databases for each patient per month. Patients were required to have at least 1 year of continuous enrollment in the MarketScan database before and after pacemaker implantation and to be ≥18 and ≤100 years of age at the time of pacemaker implantation.

To evaluate the impact of atrioventricular block (AVB) on the development of HF after pacemaker implantation, patients with a diagnosis of complete AVB (cAVB), who were presumed to have a higher burden of RV pacing, were compared with those without any degree of AVB (noAVB), who were presumed to have a lower RV pacing burden. Patients with cAVB were identified by a diagnosis of third-degree AVB (International Classification of Diseases, Ninth Revision [ICD-9] code 426.0) or an ablation of the atrioventricular junction (AVJ) (Current Procedural Terminology code 93650) in the 1 year before pacemaker implantation. Patients with an AVJ ablation occurring >1 year before pacemaker implantation or at any time after pacemaker implantation were excluded from the study. The noAVB cohort included patients who were never diagnosed with any degree of AVB (ICD-9 codes 426.0–426.1) throughout the study period.

Finally, to identify new HF diagnoses after pacemaker implantation, patients with a primary or secondary diagnosis of HF before pacemaker implantation were excluded from the study.

Patient demographics were characterized using age, sex, remote monitoring status, US region, year of pacemaker implantation, and 20 baseline (≤1 year before implant) comorbidities based on the Charlson comorbidity index. Patients were defined as active on remote monitoring if they transmitted ≥1 remote follow-up within 1 year after pacemaker implantation. US regions included Northeast, North Central, South, and West. Claims codes used for diagnoses and procedures were collected across all available fields (≤15) in the MarketScan inpatient and outpatient encounters, as shown in Table I in the Data Supplement, and validated previously.17,18 It has been previously found that the use of ICD-9 codes for the identification of HF in this manner is associated with a sensitivity of 0.76 and specificity of 0.97.18

Outcomes

New-onset HF was identified by a primary or secondary diagnosis of HF during any inpatient hospitalization or outpatient clinic visit after pacemaker implantation. The predictor variable was the presence of cAVB. To understand the time course of HF development, the primary end point was evaluated separately during an acute phase (0–6 months) and a chronic phase (6 months to 4 years) after pacemaker implantation. An administrative censoring date was set at 4 years post–pacemaker implantation.

Age Stratification

To characterize the effect of cAVB on the development of HF within various age ranges, a subanalysis was performed based on patient age at the time of pacemaker implantation. The study cohort was stratified into 5 age bins: ≤55, 56 to 65, 66 to 75, 76 to 85, and >85 years. The risk of new-onset HF in patients with cAVB versus noAVB was then compared within each of the 5 age groups for the acute and chronic phases after pacemaker implantation.

Atrial Fibrillation Subanalysis

To assess relative contributions of atrial fibrillation (AF) and cAVB on the development of HF, a second subanalysis stratified the study cohort into 4 groups based on the presence of baseline AF in the year before pacemaker implantation and the classification of cAVB. Event rates in the acute and chronic phases after pacemaker implantation were computed for patients within the 4 subgroups, as were hazard ratios (HR) for multivariable comparisons between each subgroup.

Statistics

Baseline characteristics were compared between cAVB and noAVB patients meeting inclusion criteria. Continuous variables, including follow-up duration and age, were compared using a Student t test or Mann–Whitney test if the distribution was not normal. Similarly, for the AF subanalysis, a 1-way ANOVA or a Kruskal–Wallis test was used to compare continuous variables among the 4 groups. Categorical variables, such as sex and baseline comorbidities, were compared using a χ² test.

Propensity scores for the diagnosis of cAVB were calculated for every patient in the study cohort based on a multivariable logistic regression model including all covariates used in the patient characterization.22 The unadjusted rates of new HF development (events per 100 patient-years [pt-yr]) in the cAVB and noAVB groups were calculated using the date of initial HF diagnosis and were compared using a 2-sample Poisson rate test. Event-free survival was measured by the Kaplan–Meier method, and differences between cAVB and noAVB patients were compared using a multivariable Cox proportional hazards model with propensity score adjustment. For the AF subanalysis, separate propensity scores were computed for each subgroup comparison and were used to adjust the corresponding hazard ratio. Patients were censored at the time of initial HF diagnosis, at the time of upgrade to cardiac resynchronization therapy, or at the end of MarketScan enrollment, or at the administrative censoring date. Billing codes used to identify cardiac resynchronization therapy upgrade are outlined in Table I in the Data Supplement. The proportion-al hazards assumption was tested using Schoenfeld residuals. In the
presence of nonproportional hazards, as indicated for certain comparisons within the AF subanalysis, a weighted estimation of the Cox regression provided an unbiased average hazard ratio. Statistical significance was determined using \( \alpha = 0.05 \). All analyses were performed on Revolution Analytics Revolution R Enterprise with Open Source R version 3.1.1 or SAS version 9.3. Propensity scores were computed using the LOGISTIC procedure in base SAS.

**Results**

**Study Population**

The study cohort included 21,202 patients with a mean age of 74.0±12.6 years and 54% men, of which 14,208 had noAVB and 6994 had cAVB (Figure 1). The majority of patients (80.4%) in the cAVB cohort received a diagnosis of third-degree AVB or an AVJ ablation on the same day of pacemaker implantation. Of those patients with a cAVB diagnosis or AVJ ablation occurring ≥1 days before implantation, the median time from diagnosis to implantation was 4 days (interquartile range, 1–13 days). During a median 2.35 years (interquartile range, 1.62–3.39 years) of follow-up after pacemaker implantation, 0.23% of noAVB and 0.87% of cAVB patients underwent a cardiac resynchronization therapy upgrade. Baseline characteristics are presented in Table 1. Patients with cAVB were less likely to have baseline AF (21% versus 48%) and coronary artery disease (44% versus 47%) but were more likely to present with diabetes mellitus (29% versus 24%). A higher proportion of cAVB patients were men (57% versus 53%).

**New HF After Pacemaker Implantation**

In the first 6 months after pacemaker implantation, patients with cAVB were associated with a significantly heightened risk of HF diagnosis compared with those with noAVB (adjusted hazard ratio [HR], 1.62; 95% confidence interval [CI]; 1.48–1.79; \( P < 0.001 \); Figure 2A). The unadjusted rate of incident HF in the acute phase was significantly higher for cAVB compared with noAVB patients (24.32 versus 16.54 events per 100 pt-yr, respectively; \( P < 0.001 \)). Although the risk remained elevated in the chronic phase (adjusted HR, 1.16; 95% CI, 1.08–1.25; \( P < 0.001 \)), the event rates dropped for both cAVB and noAVB patients (11.03 versus 10.16 events per 100 pt-yr, respectively; \( P = 0.022 \)), and the overall effect was attenuated (Figure 2B). Across the acute and chronic phases, minimal heterogeneity was observed within patient subgroups based on baseline comorbidities, with most stratification showing an elevated risk for new HF associated with cAVB (Figure 3A and 3B). Interestingly, in the chronic phase after pacemaker implantation, there was a significant interaction between cAVB and sex, whereby the risk of new-onset HF associated with cAVB was attenuated for women.

**Age Stratification**

Patients with cAVB and noAVB were stratified into 5 groups based on their age at the time of pacemaker implantation, as shown in Figure 4. During the duration of follow-up, the overall proportion of patients who developed HF increased with age. Within the study cohort, 11% of patients aged ≤55 years were diagnosed with new HF in the 4 years after pacemaker implantation, as well as 17% of patients aged 56 to 65 years, 23% of patients aged 66 to 75 years, 29% of patients aged 76 to 85 years, and 38% of patients aged >85 years. There was an inverse relationship between patient age and the effect of cAVB on new HF diagnosis, where cAVB patients aged ≤55 years were associated with the highest risk for developing new HF after pacemaker implantation compared with their noAVB counterparts (Figure 4A and 4B). Interestingly, within this age group, the risk was higher in the chronic phase (adjusted HR, 2.89; 95% CI, 2.03–4.12; \( P < 0.001 \)) compared with the acute phase (adjusted HR, 2.25; 95% CI, 1.39–3.64; \( P < 0.001 \)). For all other age groups, the risk of new-onset HF associated with cAVB was lower in the chronic compared with the acute phase. In particular, patients aged >85 years experienced an increased risk of new HF in the acute phase (adjusted HR, 1.59; 95% CI, 1.32–1.92; \( P < 0.001 \)) but not in the chronic phase (adjusted HR, 1.00; 95% CI, 0.86–1.16; \( P = 0.971 \)).

**AF Subanalysis**

Patients were stratified into 4 groups based on the presence of AF and cAVB. Of the 6994 cAVB patients in the study cohort, 1433 patients (21%) had an AF diagnosis in the year before pacemaker implantation, compared with 6773 patients (48%).
of the 14,208 noAVB patients. Baseline characteristics for the AF subanalysis are summarized in Table II in the Data Supplement. New-onset HF was evaluated in the acute and chronic phases for each of the 4 subgroups. Multivariable regressions showed an increased risk for new HF associated with both cAVB (acute HR, 1.62; 95% CI, 1.48–1.79; P<0.001; chronic HR, 1.16; 95% CI, 1.08–1.25; P<0.001) and baseline AF (acute unbiased average HR, 1.39; 95% CI, 1.26–1.53; P<0.001; chronic HR, 1.32; 95% CI, 1.23–1.42; P<0.001), with no interaction between the 2 conditions (Table 2). Similar to the primary results, the acute phase was associated with a higher rate of new-onset HF than the chronic phase in all 4 groups of the AF subanalysis (Table 2).

In both the acute and chronic phases after pacemaker implantation, the cohort of patients with AF and cAVB had the highest rate of new-onset HF (33.27 and 15.09 events per 100 pt-yr, respectively) and was associated with the greatest risk for developing HF compared with other groups (Figure 5A and 5B). Conversely, the group of patients without AF and with noAVB had the lowest rate of new-onset HF in both the acute and chronic phases (12.35 and 8.20 events per 100 pt-yr, respectively) and was associated with a decreased risk for new HF development compared with the other groups (Figure 5A and 5B). An intermediate risk was observed for the 2 subgroups that included patients without AF but with cAVB and those with AF and noAVB. In the acute phase, patients without AF but with cAVB had the second highest rate of new HF diagnoses (22.08 per 100 pt-yr), followed by patients with AF and noAVB (21.25 per 100 pt-yr). In the chronic phase, the order of these 2 subgroups was reversed, where patients with AF and noAVB had a higher rate of new-onset HF (12.53 per 100 pt-yr) compared with patients without AF but with cAVB (10.07 per 100 pt-yr). This finding was consistent with the results of the Cox proportional hazards model. In the acute phase, patients with AF and noAVB were associated with a reduced risk of new-onset HF compared with patients without AF but with cAVB (unbiased average HR, 0.86; 95% CI, 0.77–0.97; P=0.010), whereas in the chronic phase, this risk was reversed (HR, 1.15; 95% CI, 1.06–1.26; P=0.001).

### Discussion

In a large real-world cohort of patients without an antecedent history of HF, our data demonstrate that presumed higher burden RV pacing in the setting of a billing diagnosis of complete heart block is associated with a significantly heightened risk of developing HF. The risk associated with RV pacing begins almost immediately after pacemaker implantation, and by 6 months post-implantation, >10% of individuals with complete heart block presented with a clinical diagnosis of HF. The increased risk of HF associated with RV pacing was most pronounced among younger individuals and was potentiated by the concomitant presence of AF. These data provide the first large-scale assessment of the incidence and time course of HF in the presence of high-burden RV pacing and suggest that the adverse clinical effects of pacing-induced ventricular dysfunction may occur more quickly than previously anticipated.

Several previous studies have assessed the incidence of pacing-induced ventricular dysfunction among individuals without previous HF. In the PACE trial (Pacing to Avoid Cardiac Enlargement), among the 86 patients randomized to

### Table 1. Baseline Characteristics for the Study Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>noAVB (N=14,208)</th>
<th>cAVB (N=6,994)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postindex follow-up duration, y</td>
<td>2.39 (1.63–3.44)</td>
<td>2.27 (1.58–3.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7518 (53)</td>
<td>3996 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>6690 (47)</td>
<td>2998 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>74.0±12.4</td>
<td>73.8±13.1</td>
<td>0.187</td>
</tr>
<tr>
<td>Remote monitoring active</td>
<td>5135 (36)</td>
<td>2564 (37)</td>
<td>0.470</td>
</tr>
<tr>
<td>Year of implant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>2752 (19)</td>
<td>1267 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2010</td>
<td>3893 (27)</td>
<td>1716 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2011</td>
<td>3632 (26)</td>
<td>1853 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2012</td>
<td>3259 (23)</td>
<td>1722 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2013</td>
<td>672 (5)</td>
<td>386 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>US region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>2046 (14)</td>
<td>1391 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>North central</td>
<td>4600 (32)</td>
<td>2323 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>South</td>
<td>5158 (36)</td>
<td>2085 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>West</td>
<td>2386 (17)</td>
<td>1185 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (&lt;1)</td>
<td>10 (&lt;1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6773 (47.7)</td>
<td>1433 (20.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VT/VF</td>
<td>697 (4.9)</td>
<td>254 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6679 (47.0)</td>
<td>3077 (44.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10,535 (74.1)</td>
<td>5222 (74.7)</td>
<td>0.429</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4111 (28.9)</td>
<td>1719 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3377 (23.8)</td>
<td>2058 (29.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve disease</td>
<td>4420 (31.1)</td>
<td>2438 (34.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2424 (17.1)</td>
<td>1177 (16.8)</td>
<td>0.686</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>2904 (20.4)</td>
<td>1458 (20.8)</td>
<td>0.502</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1245 (8.8)</td>
<td>642 (9.2)</td>
<td>0.329</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>415 (2.9)</td>
<td>262 (3.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>222 (1.6)</td>
<td>96 (1.4)</td>
<td>0.313</td>
</tr>
<tr>
<td>Liver disease</td>
<td>426 (3.0)</td>
<td>230 (3.3)</td>
<td>0.269</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2340 (16.5)</td>
<td>1076 (15.4)</td>
<td>0.045</td>
</tr>
<tr>
<td>Cancer</td>
<td>1772 (12.5)</td>
<td>998 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>569 (4.0)</td>
<td>237 (3.4)</td>
<td>0.030</td>
</tr>
<tr>
<td>Depression</td>
<td>1109 (7.8)</td>
<td>476 (6.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>8 (0.1)</td>
<td>5 (0.1)</td>
<td>0.901</td>
</tr>
<tr>
<td>Hemiplegia/paraplegia</td>
<td>149 (1.0)</td>
<td>59 (0.8)</td>
<td>0.177</td>
</tr>
<tr>
<td>Obesity</td>
<td>607 (4.3)</td>
<td>362 (5.2)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data reported as n (%), median (interquartile range), and mean±SD. Continuous variables were compared using a Student t test or Mann–Whitney test for normal and non-normal distributions, respectively. Categorical variables were compared using a χ² test. VF indicates ventricular fibrillation; and VT, ventricular tachycardia.
RV pacing, the mean LVEF decreased from 61.5% to 54.8% (P<0.001) at 12 months, which was associated with a corresponding increase in LV end-systolic volume (P<0.001).

In contrast, in the group randomized to biventricular pacing, LVEF and ventricular volumes remained stable compared with baseline. Despite evidence of LV dysfunction noted at

Figure 2. Incidence of new-onset heart failure (HF) after pacemaker implantation. A, New HF in the acute phase (0–6 mo) after pacemaker implantation in patients with complete atrioventricular block (cAVB) vs those without any atrioventricular block (noAVB). B, New HF in the chronic phase (6 mo to 4 y) after pacemaker implantation in patients with cAVB vs noAVB patients.
Figure 3. Relative adjusted risk of incident heart failure (HF) within patient subgroups based on age, sex, and baseline comorbidities. A, Acute phase (0–6 mo) after de novo dual-chamber pacemaker implantation in patients with complete atrioventricular block (cAVB) vs those with no atrioventricular block (noAVB). B, Chronic phase (6 mo to 4 y) after de novo dual-chamber pacemaker implantation in patients with cAVB vs those with noAVB. P refers to the P value for the interaction between cAVB and each subgroup. CI indicates confidence interval; HR, hazard ratio; VF, ventricular fibrillation; and VT, ventricular tachycardia.
Figure 4. Risk of developing new-onset heart failure (HF) after pacemaker implantation stratified by age. A, Adjusted risk of developing new HF in the acute phase (0–6 mo) after pacemaker implantation in patients with complete atrioventricular block (cAVB) vs those with no atrioventricular block (noAVB) stratified into 5 age bins. B, Chronic phase (6 mo to 4 y).
12 months in the RV pacing group, no significant difference was observed in the incidence of HF hospitalization between the 2 groups in the first year post-implant. Although this appears discordant with our results suggesting an elevated acute incidence of HF with RV pacing, it is possible that the PACE study was underpowered to detect early HF hospitalizations. Furthermore, during long-term follow-up (mean 4.8 years) of the PACE study, 23.9% of patients in the RV pacing group experienced a HF hospitalization compared with 14.6% in the biventricular pacing group (P = 0.006). In a single-center study of 257 patients with normal baseline LVEF, PICM (defined as a drop in LVEF of ≥10% from baseline) developed in 20% of patients with an RV pacing burden of ≥20% at a mean follow-up of 3 years. In the MOST (Mode Selection Trial), among a cohort of individuals with normal LVEF and little to no HF symptoms at baseline who underwent pacemaker implantation for sinus node dysfunction, a first HF hospitalization was nearly 3-fold more likely among those with >40% RV pacing compared with those with ≤40% pacing burden during a median follow-up of 33.1 months. Moreover, by 48 months post-pacemaker implantation, ≥15% of individuals in the high-burden RV pacing group had experienced a HF hospitalization. Finally, in a nationwide cohort similar to that used in the current study, over 4 years of follow-up, pacemaker patients with AF and concurrent AVJ ablation were associated with a significantly increased risk of HF hospitalization compared with matched pacemaker patients without an ablation.

Our data and the echocardiographic data from the PACE trial are consistent in demonstrating a relatively rapid detrimental effect of RV pacing on ventricular function, which can be discerned within the first several months. Although the mechanisms of this observed effect have not been fully elucidated, an acute analysis of 12 patients with normal LVEF and forced RV pacing using short AV delays demonstrated a significant drop in LVEF within 2 hours of RV pacing and progressive deterioration of ventricular function after a week of RV pacing. Interestingly, although ventricular function improved after cessation of forced RV pacing, it remained impaired compared with baseline for 24 hours despite restoration of normal ventricular activation and synchrony. These data suggest that the acute adverse hemodynamic impact of RV pacing results not just from an abnormal pattern of electrical activation but also from a direct adverse impact on ventricular function that persists even after restoration of a normal activation sequence.

Although our data, along with others, suggest that high-burden RV pacing can have an acute detrimental effect on ventricular function and HF symptoms, not all patients seem to be equally susceptible. In a cohort of 286 patients at the Mayo clinic undergoing AVJ ablation with RV apical pacing, at a mean follow-up of 20 months, no significant change in LVEF was noted compared with baseline. Additionally, the cumulative 10-year probability of HF hospitalization after AVJ ablation was only 8%. Similar findings were reported recently from a European single-center registry, which suggested that many patients with high-burden RV pacing maintain stable LVEF with a low incidence of new-onset HF. It is likely that the adverse impact of RV pacing may affect individuals in a heterogeneous manner such that some may tolerate high RV pacing burden for many years without developing clinical HF, whereas others experience a rapid adverse impact, as noted in the acute phase of our study. Better tools are needed to identify which patients are most likely to experience a clinically relevant adverse effect of RV pacing on ventricular function. Interestingly, stratification by sex and baseline comorbidities in our study revealed minimal heterogeneity and demonstrated that cAVB is associated with increased risk for HF in the majority of patient subgroups. When stratified by age, younger patients (≤55 years) with complete heart block in our cohort were associated with an increased relative risk of incident HF compared with elderly patients. Although the absolute rate of incident HF was lowest in younger patients, RV pacing may account for a relatively large proportion of HF diagnoses among younger individuals, whereas comorbidities may weigh heavily in the development of HF in the elderly. Younger patients may also be more susceptible to HF symptoms induced by subtle changes in ventricular performance associated with RV pacing. This raises the question of whether younger patients with an anticipated high burden of ventricular pacing may be particularly good candidates for interventions designed to mitigate the adverse hemodynamic impact of RV pacing.

Table 2. Unadjusted Rates of Incident HF in Acute (0–6 mo) and Chronic (6 mo to 4 y) Phases After De Novo Dual-Chamber Pacemaker Implantation in Patients Stratified by Baseline AF and cAVB

<table>
<thead>
<tr>
<th>New HF diagnosis</th>
<th>Acute Phase</th>
<th>Chronic Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No AF cAVB</td>
<td>No AF cAVB</td>
</tr>
<tr>
<td>Total N</td>
<td>7435</td>
<td>5561</td>
</tr>
<tr>
<td>Number new HF events</td>
<td>441</td>
<td>571</td>
</tr>
<tr>
<td>New HF (per 100 pt-yr)</td>
<td>12.35</td>
<td>22.08</td>
</tr>
</tbody>
</table>

**Multivariable Cox regression**

- **cAVB: noAVB**
  - HR, 1.62 (95% CI, 1.48–1.79); P < 0.001
  - HR, 1.16 (95% CI, 1.08–1.25); P < 0.001

- **AF: no AF**
  - HR, 1.39 (95% CI, 1.26–1.53); P < 0.001
  - HR, 1.32 (95% CI, 1.23–1.42); P < 0.001

- **Interaction cAVB+AF**
  - HR, 0.93 (95% CI, 0.76–1.13); P = 0.467
  - HR, 1.04 (95% CI, 0.89–1.21); P = 0.603

**AF** indicates atrial fibrillation; cAVB, complete atrioventricular block; CI, confidence interval; HF, heart failure; HR, hazard ratio; and noAVB, patients without any degree of atrioventricular block.

*Unbiased average hazard ratio computed by weighted Cox regression.
Figure 5. Adjusted risk of new-onset heart failure (HF) stratified by atrioventricular block (AVB) and atrial fibrillation (AF). Adjusted risk of new HF in (A) the acute phase (0–6 m) and (B) the chronic phase (6 mo to 4 y) after pacemaker implantation in groups stratified by complete AVB (cAVB) and baseline atrial fibrillation (AF). ‡Unbiased average hazard ratio computed by weighted Cox regression. (1) AF vs no AF in patients with cAVB; (2) cAVB vs noAVB in patients with AF; (3) patients with AF and noAVB vs those without AF but with cAVB; (4) cAVB vs noAVB in patients without AF; and (5) AF vs no AF in patients with noAVB.
Our data also demonstrate an additive association between high-burden RV pacing and an antecedent history of AF on the development of incident HF. AF and HF frequently coexist, and each may potentiate the other. Whether the increased risk of incident HF associated with concomitant AF and atrioventricular disease noted in our cohort merely represents the effect of shared risk factors on HF or whether the presence of AF in the setting of chronic RV pacing has a truly additive detrimental effect on ventricular function remains to be fully elucidated, although both explanations are clinically relevant.

Assessing the incidence of clinically relevant ventricular dysfunction in the setting of chronic RV pacing is complicated by the presence of differing definitions for PICM and differing cut points for assessing RV pacing burden. In our analysis, we used incident HF diagnosis, evaluated in both inpatient and outpatient encounters, as the primary end point. Based on this definition, >30% of patients with complete AVB and presumably high-burden RV pacing developed HF within 4 years of pacemaker implantation. Although this definition is probably broader and more inclusive than using HF hospitalizations or a drop in LVEF as the primary end point, our data are consistent with several previous studies which, in aggregate, suggest that ≈15% to 30% of patients with high-burden RV pacing will develop a clinical diagnosis of HF or a significant drop in LVEF within 3 to 6 years after pacemaker implantation. The inclusion of outpatient encounters in assessing the adverse impact of chronic RV pacing is particularly relevant given estimates that physician visits for HF account for ≈2% of all outpatient office visits and cost the healthcare system >$2 billion per year in the United States, representing an important opportunity for curbing healthcare expenditures. Although it has been suggested that all patients undergoing pacemaker implantation with a predicted high burden of RV pacing should be implanted with a biventricular device, the results of the PREVENT-HF study and the preliminary results of the BioPace study suggest that such a broad approach to biventricular pacing may not be justified. In general, patients with PICM seem to benefit from upgrade to biventricular pacing. Whether it is detrimental to wait for ventricular dysfunction to develop before performing an upgrade and whether a cohort can be identified who may derive more benefit from biventricular pacing upfront remains to be determined. Based on our data, it may also be reasonable to perform an evaluation of LVEF at 6 months after pacemaker implantation in those with high-burden RV pacing.

However, the use of ICD-9 codes as a surrogate for pacing burden may be open to misclassification if diagnoses are incompletely coded. To mitigate this limitation, we excluded patients with intermediate levels of heart block from analysis. Because we are unable to determine the specific burden of RV pacing, we are also unable to comment on thresholds of RV pacing burden at which the risk of HF may increase.

Although our data demonstrate an additive effect on the frequency of incident HF diagnoses between the presence of AF and complete heart block, we are unable to comment on the patterns of AF (paroxysmal versus persistent versus permanent) and on the burden of AF. We are also unable to provide data on the nature of treatment for AF (ie, rate versus rhythm control) and the potential impact that AF treatment may have on RV pacing burden and HF.

Finally, mortality data are not available in the data set used for this analysis. Thus, when MarketScan enrollment ends for a particular patient, we cannot determine whether this was because of death or other reasons, such as cancellation in health insurance coverage. However, because the primary end point of an inpatient or outpatient HF diagnosis is likely to precede a HF-related mortality event, it is expected that our analysis reflects the real-world incidence of new-onset HF after pacemaker implantation.

Conclusions
In a large, national cohort of patients undergoing pacemaker implantation, those individuals with a diagnosis of complete heart block, presumed to have a high burden of RV pacing, experienced a significantly increased risk of new-onset HF. The risk of HF was most marked in the first 6 months after pacemaker implantation and was more notable in younger patients and those with a history of AF. Additional studies are needed to identify individuals most susceptible to the adverse hemodynamic effects of RV pacing and to determine which patients might benefit from upfront biventricular pacing.

Sources of Funding
Support for this project was provided by Abbott.

Disclosures
Dr Hoskins reports consulting fees from Abbott. Dr Prillinger reports salary and equity from Abbott and equity from Medtronic, Inc. G.J. Roberts reports receiving salary from Abbott. Y. Nabutovsky reports receiving salary and equity from Abbott. Dr Mittal reports consulting fees from Abbott. The other authors report no conflicts.

References


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Circ Cardiovasc Qual Outcomes. 2017;10:
doi: 10.1161/CIRCOUTCOMES.117.003564
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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