Adverse Effect of Ventricular Pacing on Heart Failure and Atrial Fibrillation Among Patients With Normal Baseline QRS Duration in a Clinical Trial of Pacemaker Therapy for Sinus Node Dysfunction

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Background—Dual-chamber (DDDR) pacing preserves AV synchrony and may reduce heart failure (HF) and atrial fibrillation (AF) compared with ventricular (VVIR) pacing in sinus node dysfunction (SND). However, DDDR pacing often results in prolonged QRS durations (QRSd) as the result of right ventricular stimulation, and ventricular desynchronization may result. The effect of pacing-induced ventricular desynchronization in patients with normal baseline QRSd is unknown.

Methods and Results—Baseline QRSd was obtained from 12-lead ECGs before pacemaker implantation in MOST, a 2010-patient, 6-year, randomized trial of DDDR versus VVIR pacing in SND. Cumulative percent ventricular paced (Cum%VP) was determined from stored pacemaker data. Baseline QRSd <120 ms was observed in 1339 patients (707 DDDR, 632 VVIR). Cum%VP was greater in DDDR versus VVIR (90% versus 58%, P<0.001). Cox models demonstrated that the time-dependent covariate Cum%VP was a strong predictor of HF hospitalization in DDDR (hazard ratio [HR], 2.99 [95% CI, 1.15 to 7.75] for Cum%VP >40%) and VVIR (HR 2.56 [95% CI, 1.48 to 4.43] for Cum%VP >80%). The risk of AF increased linearly with Cum%VP from 0% to 85% in both groups (DDDR, HR 1.36 [95% CI, 1.09, 1.69]; VVIR, HR 1.21 [95% CI 1.02, 1.43], for each 25% increase in Cum%VP). Model results were unaffected by adjustment for known baseline predictors of HF hospitalization and AF.

Conclusions—Ventricular desynchronization imposed by ventricular pacing even when AV synchrony is preserved increases the risk of HF hospitalization and AF in SND with normal baseline QRSd. 

Key Words: pacing ■ heart failure ■ fibrillation

The optimal pacing mode for symptomatic bradycardia caused by sinus node dysfunction (SND) is still debated. Though maintenance of atrioventricular (AV) synchrony afforded by dual-chamber pacing is intuitively superior to ventricular pacing, this has been surprisingly difficult to prove. Large randomized clinical trials have reached consensus that there is no survival benefit in patients that are dual-chamber paced. However, the same trials have produced inconsistent results regarding the effect of pacing mode on cardiovascular morbidity.1-3 One possible explanation is that ventricular desynchronization imposed by right ventricular apical pacing in the dual-chamber mode has adverse long-term effects that mitigate the benefit of AV synchrony.

This study tested the hypothesis that ventricular desynchronization imposed by right ventricular apical pacing even when AV synchrony is preserved increases the risk of heart failure hospitalization (HFH) and atrial fibrillation (AF) in patients with SND and normal baseline QRS duration.

Methods

The study population was extracted from the MOde Selection Trial (MOST), a 6-year, prospective, randomized comparison of single-chamber ventricular rate modulated (VVIR) pacing versus dual-chamber rate modulated (DDDR) pacing in 2010 patients with SND.4 Eligible patents received DDDR pacing systems for SND and were in sinus rhythm at the time of their random assignment.
Ventricular pacing leads were placed at the right ventricular apex. For both groups, the lower rate was programmed to ≥60 and the upper rate ≥110 beats per minute. For the DDDR group, the programmed AV delay was recommended to be in the optimal physiological range (120 to 200 ms).

Before pacemaker implantation, baseline demographic and clinical data were collected and QRS duration was determined from 12-lead ECGs. Normal QRS duration was defined as <120 ms. Abnormal AV conduction (including first-degree AV block) was present in 16% of DDDR and 20% of VVIR patients.

Median follow-up was 33.1 months. The MOST secondary end points of HFH and AF were used in this study. A Clinical Events Committee blinded to assigned pacing mode adjudicated all first HFHs. Subsequent HFHs were defined by a primary diagnosis-related grouping (DRG) code of congestive heart failure. An ECG Core Laboratory, blinded to pacing mode, confirmed incident cases of AF.

Percent ventricular paced was determined from stored pacemaker diagnostic data at each follow-up visit. For each patient, cumulative percent ventricular paced (Cum%VP) from random assignment to each day of follow-up was calculated by (1) finding, for each visit, the mean percent ventricular paced over all visits up to and including that visit, weighted by the number of days between visits, and (2) using linear interpolation to determine the values for days between visits. Cumulative percent atrial paced (Cum%AP) was calculated similarly.

For summarizing event rates, Cum%VP categories were created by using the value at the time of the event for patients with events and the value at the end of follow-up for patients without events.

Statistical Analysis
Cum%VP was compared between pacing modes by means of a Wilcoxon rank-sum test.

The relation of Cum%VP to first HFH and first incidence of AF was assessed by means of Cox proportional hazards models, with time to event as the dependent variable and Cum%VP as a time-dependent covariate. HFH models were extended to include multiple HFHs by use of Cox models that allow multiple events per patient.

Both unadjusted models (Cum%VP as the only predictor) and adjusted models (adjusted for other known baseline predictors, determined from multivariable analysis on all MOST patients) were generated. HFH models were adjusted for prior heart failure, ejection fraction, antiarrhythmic therapy, and Karmofsky score. Other potential adjustment variables—cardiac medications (aspirin, ACE inhibitors, diuretics, β-blockers, calcium channel blockers), baseline rhythm, left ventricular hypertrophy, hypertension, and lower pacing rate—were found to be unrelated to HFH and were not included in any model. AF models were adjusted for prior AF, antiarrhythmic therapy, congestive heart failure, mitral regurgitation, and AV block. Cum%AP was used in adjusted AF models in DDDR patients.

Initial examination of the data showed, within each pacing mode, that the relation between Cum%VP and both end points could be characterized by using 2-part linear spline functions, for example, the relations were allowed to have different slopes over different parts of the range of percent pacing. For each end point and each pacing mode, the point at which the slope of the risk relation changed was chosen to give the best model fit. With the use of the Cox model, tests of whether the slope parameters were different from zero on either side of the change point were performed to assess whether risk was level over some part of the range and whether a more parsimonious model could be used with values truncated above or below a certain point. Because data were sparse over some parts of the range, and as an alternative way of describing the results, models were used for the HFH end point that categorized Cum%VP as being above or below the change point. Relative risk is expressed as a hazard ratio (95% confidence interval) (HR [CI]). In all models, patients who were permanently changed to the other pacing mode were censored at the time of crossover.

Because of the difficulty in displaying time-dependent covariates graphically, percent ventricular paced during the first 30 days, which correlated well with Cum%VP over all of follow-up (r=0.76), was used to define percent pacing groups for Kaplan-Meier plots. For HFH plots, groups were defined by the points of change in the risk relations for the models (above). For the AF plots, because there were no points of change in the slope of the risk relation within the range of interest, groups of ≤40%, 40% to 70%, and 70% to 90% paced were chosen as dividing the range roughly into thirds.

Results
Baseline QRS Duration and Cum%VP
Baseline QRS duration and Cum%VP data were available in 1732 of 2010 (86.2%) patients. Baseline QRS duration <120 ms was observed in 1339 of 1732 (77.3%). Of these 1339, 707 (52.8%) were randomly assigned to DDDR and 632 (47.2%) to VVIR.

Most patients had normal left ventricular function (median ejection fraction, 55%) and mild or no symptoms of congestive heart failure (Table 1). More than half had a history of atrial tachycardia. The baseline PR interval was normal (<200 ms) or mildly prolonged in most patients.

Cum%VP was significantly higher in the DDDR versus the VVIR group (median [25th, 75th percentile], 90% [57, 99] versus 58% [20, 86]; P=0.001). Fifty percent of the DDDR group were ventricular paced continuously or near continuously (>90% of the time) compared with only 20% in the VVIR group. Reciprocally, a smaller percentage of the DDDR group (7%) was infrequently ventricular paced (<10% of the time) compared with the VVIR group (15%).

The higher incidence of Cum%VP in the DDDR group is due to the overlap of baseline PR intervals with programmed AV delays in most patients.

Heart Failure Hospitalization
Of 1339 patients in this analysis, 128 (9.6%) had at least one adjudicated HFH. The DDDR and VVIR paced groups demonstrated a somewhat different pattern of increase in rate

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### TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Baseline Characteristic*</th>
<th>DDDR (n=707)</th>
<th>VVIR (n=632)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73 (66, 79)</td>
<td>74 (67, 80)</td>
</tr>
<tr>
<td>Female</td>
<td>50% (356)</td>
<td>51% (324)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>26% (185)</td>
<td>21% (133)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>57 (50, 62)</td>
<td>55 (50, 63)</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>18% (125)</td>
<td>16% (100)</td>
</tr>
<tr>
<td>NYHA CHF class I or II</td>
<td>83% (580)</td>
<td>87% (541)</td>
</tr>
<tr>
<td>PCI</td>
<td>13% (93)</td>
<td>13% (79)</td>
</tr>
<tr>
<td>CABG</td>
<td>19% (131)</td>
<td>18% (115)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>47% (331)</td>
<td>40% (254)</td>
</tr>
<tr>
<td>Other atrial tachycardia</td>
<td>20% (142)</td>
<td>21% (131)</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>180 (160, 200)</td>
<td>190 (160, 220)</td>
</tr>
</tbody>
</table>

*Categorical variables are percent (No.); continuous variables are median (25th, 75th percentiles).
of HFH with Cum%VP (Table 2). The overall rate of HFH in the two pacing modes was similar (10% DDDR, 9% VVIR).

In the DDDR mode, the risk of HFH increased with increased Cum%VP from 0% pacing up to \( \approx 40\% \) and was level for 40% to 100% pacing (test for non-zero slope, \( P=0.84 \)) (Figure 1a). In a model that truncated values above 40%, the adjusted HR [CI] was 1.54 [1.01 to 2.36] (\( P=0.046 \)), indicating a 54% relative increase in risk of HFH for each 10% increase in Cum%VP up to 40%.

An adjusted model that included Cum%VP as a categorical variable (\( >40\% \) versus \( \leq 40\% \)) had an HR [CI] of 2.60 [1.05 to 6.47] (\( P=0.040 \)), indicating that ventricular pacing \( >40\% \) of the time in the DDDR mode was associated with a 2.6-fold increased risk of HFH compared with pacing \( \leq 40\% \) of the time (Table 3).

In the VVIR mode, the shape of the relation between the risk of HFH and Cum%VP was different versus DDDR mode. Risk was level between 0% and 80% Cum%VP (test for non-zero slope \( P=0.28 \)) and increased with increased Cum%VP from 80% pacing to 100% (Figure 1b). In a model that truncated values below 80%, the adjusted HR [CI] was 1.96 [1.39, 2.77] (\( P=0.0001 \)), indicating a 96% increased relative risk for each 10% increase in Cum%VP \( >80\% \). An adjusted model that included Cum%VP as a categorical variable (\( >80\% \) versus \( \leq 80\% \)) had an HR [CI] of 2.50 [1.44 to 4.36] (\( P=0.0012 \)), indicating that ventricular pacing \( >80\% \) of the time in the VVIR mode was associated with a 2.5-fold increased risk of HFH compared with pacing \( \leq 80\% \) of the time (Table 3).

Of the 128 patients who had at least one adjudicated HFH, 38 (29.7%) had \( \leq 1 \) (range, 1 to 6; total, 66) subsequent HFHs. Thus, 194 HFHs were used to assess the relation of Cum%VP to HFH, taking all occurrences into account.

Kaplan-Meier plots relating time to first HFH by Cum%VP show an early, sustained and increasing incidence of HFH among DDDR patients with Cum%VP \( >40\% \) compared with \( \leq 40\% \) and among VVIR patients with Cum%VP \( >80\% \) compared with \( \leq 80\% \) (Figure 2, a and b).

### Table 2. Rates of Heart Failure Hospitalization and Atrial Fibrillation by Pacing Mode and Cumulative Percent Ventricular Paced

<table>
<thead>
<tr>
<th>Cum%VP</th>
<th>DDDR (n=707)</th>
<th>VVIR (n=632)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFH, n (%)</td>
<td>AF, n (%)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>48 (2)</td>
<td>49 (16)</td>
</tr>
<tr>
<td>10%–50%</td>
<td>110 (10)</td>
<td>112 (19)</td>
</tr>
<tr>
<td>50%–90%</td>
<td>188 (9)</td>
<td>193 (32)</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>361 (12)</td>
<td>347 (17)</td>
</tr>
<tr>
<td>Total</td>
<td>707 (10)</td>
<td>701 (21)</td>
</tr>
</tbody>
</table>

Cum%VP indicates cumulative percent ventricular paced; HFH, heart failure hospitalization; and AF, atrial fibrillation.

### Table 3. Cox Models of the Effect of Cumulative Percent Ventricular Paced on Heart Failure Hospitalization

<table>
<thead>
<tr>
<th>Pacing Mode</th>
<th>Hazard Ratio (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cum%VP ( &gt;40% ) vs ( \leq 40% )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDDR First HFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model*</td>
<td>3.01 (1.21, 7.46)</td>
<td>0.018</td>
</tr>
<tr>
<td>Adjusted model†</td>
<td>2.60 (1.05, 6.47)</td>
<td>0.040</td>
</tr>
<tr>
<td>All HFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model*</td>
<td>3.66 (1.44, 9.30)</td>
<td>0.0064</td>
</tr>
<tr>
<td>Adjusted model†</td>
<td>2.99 (1.15, 7.75)</td>
<td>0.024</td>
</tr>
<tr>
<td>Cum%VP ( &gt;80% ) vs ( \leq 80% )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVIR First HFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model*</td>
<td>3.13 (1.86, 5.28)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Adjusted model†</td>
<td>2.50 (1.44, 4.36)</td>
<td>0.0012</td>
</tr>
<tr>
<td>All HFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model*</td>
<td>3.60 (1.93, 6.70)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Adjusted model†</td>
<td>2.56 (1.48, 4.43)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Cum%VP indicates cumulative percent ventricular paced; HFH, heart failure hospitalization.

*Cum%VP as the only predictor.
†Adjusted for other known predictors of HFH.
The rates of AF increased in both pacing modes as Cum%VP increased up to 80% to 85%, above which the incidence tapered off (Table 2). The overall rate of AF was slightly higher in the VVIR (24%) versus the DDDR (21%) group. There are 6 fewer DDDR patients in the AF (701) versus the HFH (707) analysis because 6 patients had AF on the same day as pacemaker implantation and were excluded from AF analysis.

Modeling confirmed this pattern, as the risk of AF showed an increasing relation with increased Cum%VP from 0% pacing up to 80% or 85% pacing in both pacing modes (Table 4) (Figure 1, c and d). The risk of AF increased by 1% for each 1% increase in Cum%VP up to 85% in DDDR. The risk of AF increased by 0.7% for each 1% increase in Cum%VP up to 80% in VVIR.

Kaplan-Meier plots relating time to first episode of AF by Cum%VP show an early, sustained and increasing incidence of AF among DDDR and VVIR patients with increasing Cum%VP (Figure 3, a and b).

**Discussion**

This is the first report of a strong association between ventricular pacing in the DDDR mode and heart failure in a clinical trial of pacemaker therapy for symptomatic SND. Despite maintenance of AV synchrony, ventricular pacing in the DDDR mode >40% of the time conferred a 2.6-fold increased risk of HFH compared with less pacing among similar patients with normal baseline QRS duration. This risk increased to 3-fold when multiple HFHs were considered. This provides some evidence that highly paced patients are not only at greater risk for HFH but are also hospitalized for heart failure more often. Ventricular pacing in the VVIR mode >80% of the time was also associated with a significant increased risk of HFH compared with less pacing among similar patients. This latter observation is consistent with clinical trials that demonstrated a relative increased incidence of heart failure in SND treated with ventricular versus atrial pacing. Our observations may explain the previously puzzling dichotomy between the striking benefits of atrial pacing reported by Andersen et al and the more modest benefits of dual-chamber pacing reported by Connolly et al and Lamas et al. This increased risk of HFH associated with increased Cum%VP in the DDDR and VVIR modes persisted when the models were adjusted for all other known baseline predictors of HFH in the study population.

The average risk of HFH in the study population was ≈10%. The lowest rate of HFH grouped by Cum%VP and pacing mode was 2% among the DDDR group who were paced <10% of the time. The shape of the relation between Cum%VP and risk of HFH was different between DDDR and VVIR pacing modes. The risk was level above a certain Cum%VP (40%) in the DDDR mode and level below a certain percentage (80%) in the VVIR mode. These results imply that the risk of HFH in the DDDR mode does not increase with further increases in Cum%VP >40%, but this risk might be reduced to ≈2% if ventricular pacing is minimized. In contrast, the relative risk of HFH in the VVIR mode cannot be reduced regardless of minimization of ventricular pacing, and this risk is increased by as much as 2.5-fold when Cum%VP exceeds 80%.

Ventricular pacing was also associated with an increased risk of AF. The best models demonstrated a linearly increasing risk of AF with Cum%VP in DDDR and VVIR modes up to ≈80% to 85%. The magnitude of increased risk was ≈1% for each 1% increase in Cum%VP and was similar between pacing modes. This increased risk of AF associated with increased Cum%VP in both modes persisted when the models were adjusted for all other known baseline predictors of AF in the study population.
The reduction in heart failure and AF in atrial versus ventricular pacing for SND has been attributed to the physiological benefit of maintaining AV synchrony during pacing. Long-term asynchronous ventricular pacing causes atrial electrical remodeling and increased atrial diameters resembling that associated with chronic AF that are reversible with restoration of AV synchrony.

However, despite maintenance of AV synchrony, similar benefits of dual-chamber pacing versus ventricular pacing have been difficult to demonstrate in clinical trials. The PAcemaker Selection in the Elderly (PASE) Trial showed a trend toward improved quality of life and fewer clinical end points (AF and HFH) among patients with SND treated with DDDR versus VVIR pacing. The Canadian Trial Of Physiologic Pacing (CTOPP) reported a modest reduction of AF among patients with any diagnosis (heart block, SND) treated with DDDR versus VVIR pacing. MOST demonstrated modest reductions in HFH and AF with DDDR versus VVIR pacing in SND.

Though DDDR pacing maintains a physiological AV relation compared with ventricular pacing, this may come at the cost of a normal ventricular activation sequence compared with atrial pacing. The results of the present study strongly suggest that the discrepancy between the relative benefits of atrial compared with dual-chamber pacing in SND is due to adverse effects of asynchronous electrical activation of the left ventricle imposed by right ventricular apical pacing. Right ventricular apical pacing produces a left ventricular electrical activation sequence resembling left bundle-branch block. The resulting alteration in mechanical activation may result in impaired hemodynamic performance and mitral regurgitation. Right ventricular apical pacing causes chronic changes in regional myocardial perfusion, cellular structure, and ventricular geometry that may impair ventricular performance. The increased incidences of HFH and AF observed in the more frequently ventricular paced patients in the present study possibly relate to ventricular desynchronization.

The adverse effect of ventricular pacing on heart failure was modest, reflecting the fact that the vast majority of patients had normal left ventricular function and no prior history of symptomatic heart failure at baseline. It is possible that the impact of forced ventricular desynchronization during DDDR pacing on patients with reduced ventricular function and heart failure would be more dramatic. One retrospective study reported symptomatic deterioration in heart failure after institution of ventricular pacing in the DDDR mode among ICD patients.

Our results have potentially important clinical implications. The majority of patients with SND who receive pacemakers or ICDs, including those with heart failure and reduced ventricular function, have a normal ventricular activation sequence reflected in QRS duration. DDDR pacing typically utilizes AV delays in the range of 120 to 200 ms that result in a high percentage of ventricular pacing during normal operation. Ventricular desynchronization caused by right ventricular apical pacing in the DDDR mode may increase the risk of heart failure and AF, particularly when imposed on the failing left ventricle. Such risks may be reduced by minimal ventricular pacing strategies that preserve the normal ventricular activation sequence as much as possible.

Study Limitations
This study does not demonstrate a definitive link between ventricular desynchronization imposed by ventricular pacing in the DDDR mode and HFH and AF. We did not measure indexes of left ventricular performance over time or paced QRS durations. It is possible that ventricular fusion or pseudofusion occurred in some patients. Theoretically, however, this would have only weakened the association of ventricular pacing with adverse outcomes. Prospective, randomized trials comparing conventional DDDR pacing, new dual-chamber minimal ventricular pacing techniques that promote intrinsic AV nodal conduction and preserve normal ventricular activation, and perhaps cardiac resynchronization therapy in patients with AV block are necessary to confirm these preliminary observations.

Conclusions
Our study suggests that ventricular desynchronization imposed by right ventricular apical pacing even when AV synchrony is preserved increases the risk of heart failure and AF in patients with SND and normal baseline QRS duration. Further research is necessary to clarify the role of “electrical unloading” of the left ventricle using minimal ventricular pacing strategies in SND and normal QRS duration, particu-
larly among patients with reduced ventricular function and symptomatic heart failure.

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References
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