Heart Failure During Cardiac Pacing

Michael O. Sweeney, MD; Anne S. Hellkamp, MS

Background—Right ventricular apical (RVA) pacing creates abnormal left ventricular contraction, hypertrophy, and reduced pump function. The adverse effects of ventricular desynchronization may explain the association of RVA pacing with an increased risk of heart failure hospitalization (HFH) in clinical trials.

Methods and Results—Baseline and postimplantation variables were used to predict HFH in the Mode Selection Trial, a 2010-patient, 6-year trial of dual-chamber (DDDR) versus ventricular (VVIR) pacing in sinus node dysfunction. A Cox model showed that New York Heart Association (NYHA) class at baseline and follow-up predicted HFH (hazard ratio [HR], 3.99; 95% confidence interval [CI], 2.74–5.79 for NYHA class III/IV and HR, 2.17; 95% CI, 1.54–3.04 for NYHA class II versus class I); other predictors were heart failure (HR, 2.30; 95% CI, 1.70–3.11), atrioventricular (AV) block (HR, 1.48; 95% CI, 1.11–1.97), and myocardial infarction (MI) (HR, 1.37; 95% CI, 1.00–1.86). Postimplantation predictors were VVIR cumulative percent ventricular pacing (Cum%VP) >80 (HR, 3.58; 95% CI, 1.72–7.45), DDDR Cum%VP >40 or VVIR Cum%VP ≤80 (HR, 1.81; 95% CI, 0.94–3.50) versus DDDR Cum%VP ≤40; whether QRS duration (QRSd) was paced or spontaneous (HR, 2.21; 95% CI, 1.39–3.54; spontaneous versus paced); and drugs for atrial fibrillation (HR, 1.60; 95% CI, 1.19–2.15). Low baseline ejection fraction (EF) and postimplantation RVA-paced or spontaneous QRSd predicted HFH; the increased risk with QRSd was steeper for normal versus low EF (HR, 1.18; 95% CI, 1.11–1.27; versus HR, 1.08; 95% CI, 1.01–1.15; for a 10-ms increase); at a QRSd of ~200 ms, normal- and low-EF patients had equivalent risk. HFH risk nearly doubled when VVIR Cum%VP was ≤80 or DDDR Cum%VP was >40 versus DDDR Cum%VP ≤40 and was additive with other risk factors.

Conclusions—Differences in HFH risk can be explained by interactions between substrate (atrial fibrillation, AV conduction, heart failure, MI, EF) and pacing promoters (ventricular desynchronization-paced QRSd and Cum%VP, and AV desynchronization-pacing mode). Management of RVA pacing is important for reducing the risk of HFH, particularly among patients with low EF and heart failure. (Circulation. 2006;113:2082-2088.)

Key Words: heart failure ■ pacemakers ■ pacing

Right ventricular apical (RVA) pacing results in a left ventricular (LV) electrical activation sequence resembling left bundle-branch block.1 The resulting electrical asynchrony is manifest in a prolonged QRS duration (QRSd) due to slow myocardial conduction. Consequently, LV contraction is altered, and significant interventricular and intraventricular dyssynchrony may occur.2 Ventricular desynchronization imposed by RVA pacing results in chronic LV remodeling, including asymmetric hypertrophy and redistribution of cardiac mass,3,4 mitral regurgitation,5,2 increased left atrial diameter,8 and reduced ejection fraction (EF).8–10 These adverse effects on ventricular structure and function likely explain the association of RVA pacing, independent of atrioventricular (AV) synchrony, with increased risks of atrial fibrillation (AF) and heart failure in randomized, clinical trials (RCTs) of pacemaker therapy8,11 and additionally, of ventricular arrhythmias and death during implantable cardioverter-defibrillator (ICD) therapy.12,13

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Nonetheless, the majority of patients who receive pacemakers for standard bradycardia indications do not experience heart failure that can be attributed to RVA pacing, even at high frequencies. In the Mode Selection Trial (MOST), only ~10% of 2010 patients randomized experienced at least 1 heart failure hospitalization (HFH) during a median follow-up of 3 years.11

The purpose of the present study was to identify the clinical variables predictive of HFH in MOST, a prospective, randomized trial of single- versus dual-chamber pacemaker therapy for sinus node dysfunction.

Methods

The MOST was a 6-year, prospective, randomized comparison of ventricular (VVIR) pacing versus dual-chamber (DDDR) pacing in 2010 patients with sinus node dysfunction.14 The baseline demographic and clinical characteristics of the study population have previously been described.11,14,15

Received December 15, 2005; revision received February 4, 2006; accepted February 24, 2006.

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Guest Editor for this article was N.A. Mark Estes III, MD.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.105.608356

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TABLE 1. Preimplantation and Postimplantation Variables

<table>
<thead>
<tr>
<th>Preimplantation and Postimplantation Variables</th>
<th>Before implantation</th>
<th>After implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized pacing mode</td>
<td>DDDR 50% (1014)</td>
<td>Cum%VP 78 (43, 96)</td>
</tr>
<tr>
<td></td>
<td>VVIR 50% (996)</td>
<td>DDDR (overall) 91 (64, 99)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20% (404)</td>
<td>VVIR (overall) 60 (29, 87)</td>
</tr>
<tr>
<td>MI</td>
<td>26% (522)</td>
<td>DDDR ≤40 7% (145)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I 44% (877)</td>
<td>DDDR &gt;40 or VVIR ≤80 77% (1541)</td>
</tr>
<tr>
<td></td>
<td>II 40% (808)</td>
<td>VVIR &gt;80 16% (324)</td>
</tr>
<tr>
<td></td>
<td>III/IV 16% (325)</td>
<td>Postimplantation QRSd</td>
</tr>
<tr>
<td></td>
<td>Low EF 27% (540)</td>
<td>Paced 62% (1251)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62% (1248)</td>
<td>Paced QRSd 160 (146, 178)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>29% (586)</td>
<td>Unpaced 38% (739)</td>
</tr>
<tr>
<td>AV block</td>
<td>21% (413)</td>
<td>Unpaced QRSd 95 (84, 112)</td>
</tr>
<tr>
<td>AF</td>
<td>46% (917)</td>
<td>Antiarrhythmic drugs for AF 34% (689)</td>
</tr>
<tr>
<td>Baseline QRSd, ms</td>
<td>96 (84, 112)</td>
<td>AF reported 45% (895)</td>
</tr>
<tr>
<td>Baseline QRSd ≥120 ms</td>
<td>22% (446)</td>
<td>Worse NYHA class 40% (800)</td>
</tr>
</tbody>
</table>

Values are given as % (n) or median (Q1, Q3).

Eligible patients received DDDR pacing systems for sinus node dysfunction and were in sinus rhythm at the time of implantation. Ventricular pacing leads were placed at the RVA. After successful pacing system implantation, the programmed pacing mode was randomized (DDDR versus VVIR). For both groups, the lower rate was programmed to ≥60 bpm, and the upper rate was programmed to ≥110 bpm. For the DDDR group, the programmed AV delay was recommended to be in the optimal physiological range (120 to 200 ms) for RVA stimulation.16

Baseline clinical data included the QRSd obtained from automated measurements from 12-lead ECGs. Postimplantation QRSd was similarly obtained at 1 month or the first available after implantation up to 3 months and again at 1 year. Median follow-up was 33.1 months. The most secondary end point of HFH was used in this study.14 A clinical events committee blinded to the assigned pacing mode adjudicated all first HFHs.

Statistical Analysis

Variable Definitions

Predictors considered in this analysis are listed in Table 1. New York Heart Association (NYHA) heart failure classes III and IV were combined into a single group because of the small number of class IV patients (n = 36). Low ejection fraction (EF) was defined as an EF <50% (among 1135 patients with EF data) or a clinical impression of any LV dysfunction. Revascularization included coronary artery bypass surgery and angioplasty. A normal QRSd (nQRSd) was defined as being <120 ms; a prolonged QRSd (pQRSd) was defined as lasting ≥120 ms.17 "AF reported" includes any AF episodes reported on the case report form during the follow-up period, including those detected solely by the presence of atrial high-rate episodes logged by the pacemaker.16,19

Percent ventriculaly paced was determined from stored pacemaker diagnostic data at each follow-up visit. For each patient, the cumulative percent ventriculaly paced (Cum%VP) from the time of random assignment to each day of follow-up was calculated by (1) finding, for each visit, the mean percent ventriculaly 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.

Missing Data and Imputation

The level of missing data for baseline variables was <2% for all variables except for QRSd, which was missing in 7% (125 patients). The level of missing data for postimplantation variables was <2% for all variables except for Cum%VP and QRSd, which were missing in 5% (97 patients) and 13% (237 patients), respectively.

Missing data were imputed by using a single conditional mean imputation.20 For each variable that had any missing data, a predictive model was created among patients with no missing data; that model was then used to predict values for patients who were missing those data. The datasets for imputation contained more variables than those listed in Table 1 (37 baseline and 20 after implantation), including comorbidities and other related variables.

Summary Statistics

Preimplantation and postimplantation variables are summarized as medians (25th and 75th percentiles) for continuous variables and as percentages (number) for categorical variables. QRSd values were compared between subgroups with Wilcoxon rank-sum tests.

Modeling the Risk of HFH

The end point of the first adjudicated HFH was assessed in a Cox proportional-hazards model that included the candidate predictors in Table 1. Based on our earlier work,11 pacing mode and Cum%VP were combined into a 3-category variable with classes DDDR/Cum%VP ≤40; DDDR/Cum%VP >40 or VVIR/Cum%VP ≤80; and VVIR/Cum%VP >80. Because the intent of modeling was to identify all risk factors associated with HFH, regardless of when they occurred, time-dependent covariates, which allowed the patients' data values to change over the course of follow-up, were used whenever possible. These included pacing mode/Cum%VP, postimplantation QRSd (paced or unpaced), antiarrhythmic therapy for AF, reported AF, and NYHA class. Interactions between QRSd and randomized pacing mode/Cum%VP and the other predictors were tested to determine whether their risk relations with HFH were affected by other variables. Model performance was assessed by calculating a c-index.21 A pair of patients was considered usable for this calculation if (1) the ordering of outcomes could be determined and (2) the linear predictor (Xβ) at each time point for 1 patient in the pair was higher than each Xβ for the other patient. The pair was classified as concordant if the patient with the lower Xβs (ie, lower probability of HFH) had the longer HFH-free time.

Predictions of 2-year HFH rates were made from the Cox model for “typical” patients of different types and different pacing mode/Cum%VP categories. These patient types were defined by heart failure, myocardial infarction (MI), EF, and baseline and postimplantation QRSd values. For each type, other variables in the model were set to the most common value among patients of that type.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
## Results

### Clinical Variables Associated With HFH

Candidate preimplantation and postimplantation predictors of HFH are shown in Table 1. Fewer than approximately one third of the patients had symptomatic heart failure and/or clinical evidence of a substrate for systolic heart failure (ie, MI, low EF). The vast majority of patients had normal ventricular conduction at enrollment (QRSd ≤120 ms), but the postimplantation QRSd value was significantly prolonged in nearly two thirds of patients, owing to ventricular pacing. Overall Cum%VP was significantly higher in the DDDR versus the VVIR group, as expected, because ventricular pacing is synchronized to atrial events in the DDDR mode and the baseline PR intervals overlapped with the programmed AV delay in most patients.

### HFH During Cardiac Pacing

The results of the Cox proportional-hazards model for a first HFH based on 227 events are shown in Table 2. The c-index was 0.85, indicating that the model has high ability to discriminate higher- from lower-risk patients.

The strongest independent predictor of HFH was increasing NYHA functional class. Low EF, heart failure, AV block, and MI constituted the remaining preimplantation independent predictors of HFH. The unadjusted hazard ratio (HR) for MI was 2.42 (95% confidence interval [CI], 1.86 to 3.14; P=0.001). After adjustment for EF and heart failure, the HR declined to 1.37 but remained significant, indicating that the increased relative risk of HFH from MI cannot be explained solely by an association with heart failure and EF. Baseline QRSd, history of hypertension, revascularization, and preimplantation or postimplantation AF were not significant in the adjusted model.

A high frequency of ventricular pacing (>80%) in the VVIR mode was the most potent postimplantation predictor of HFH (Table 2). Any amount of ventricular pacing ≤80% in the VVIR mode or >40% in the DDDR mode was associated with an increased risk of HFH compared with ≤40% ventricular pacing in the DDDR mode. Furthermore, there was no difference in the risk of HFH between VVIR ≤80% and DDDR >40% when these 2 groups were placed in the model separately (P=0.75, HR=1.77 for DDDR >40% versus 1.87 for VVIR ≤80% when each was compared with DDDR ≤40%). None of the interactions with pacing mode/Cum%VP were significant (all P>0.40). Postimplantation QRSd was also a strong predictor of HFH (Table 2). The risk of HFH increased incrementally with increasing QRSd, independent of whether the pQRSd occurred spontaneously or was caused by RVA pacing. However, the risk of HFH was always ≥2-fold higher for any given value of pQRSd that occurred spontaneously versus that due to RVA pacing. The increased risk of HFH associated with increasing QRSd was slightly greater in patients with a normal versus a low EF. New antiarrhythmic therapy for AF was also a postimplantation predictor of HFH.

### QRSd and HFH Risk

The shape of the relation between QRSd and risk of HFH is shown in Figure 1. The median paced QRSd was significantly longer than nonpaced QRSd (160 versus 95, P=0.001). However, there was no statistically significant difference in the slope of the relation between nonpaced QRSd and paced QRSd. This can be interpreted to mean that for each increasing value of QRSd, the relative increased risk of HFH was equivalent, regardless of whether the prolonged QRSd was due to RVA pacing or whether it occurred spontaneously.

### EF, QRSd, and HFH Risk

The shape of the relation between baseline EF, QRSd, and risk of HFH is shown in Figure 2. Baseline EF was the only independent predictor of HFH in the Cox model that demonstrated a significant interaction with QRSd (P=0.006). The effect of this interaction was that the risk of HFH with

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**TABLE 2. Cox Model of First HFH During Cardiac Pacing**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.99, III/IV vs I</td>
<td>2.74–5.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Low EF</td>
<td>3.07, when QRSd=80 ms</td>
<td>1.72–5.49</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.11, when QRSd=120 ms</td>
<td>1.44–3.10</td>
<td>0.001</td>
</tr>
<tr>
<td>MI</td>
<td>1.45, when QRSd=160 ms</td>
<td>1.06–1.98</td>
<td></td>
</tr>
<tr>
<td>Postimplantation variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VVIR Cum%VP &gt;80</td>
<td>3.58, vs DDDR Cum%VP ≤40</td>
<td>1.72–7.45</td>
<td>0.001</td>
</tr>
<tr>
<td>DDDR Cum%VP &gt;40, VVIR Cum%VP ≤40</td>
<td>1.81, vs DDDR Cum%VP ≤40</td>
<td>0.94–3.50</td>
<td></td>
</tr>
<tr>
<td>Unpaced vs paced for given value of postimplantation QRSd</td>
<td>2.21</td>
<td>1.39–3.54</td>
<td>0.001</td>
</tr>
<tr>
<td>Postimplantation QRSd, paced or unpaced</td>
<td>1.18 for each 10-ms increase when EF is normal</td>
<td>1.11–1.27</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1.08 for each 10-ms increase when EF is low</td>
<td>1.01–1.15</td>
<td></td>
</tr>
<tr>
<td>New antiarrhythmic drugs for AF</td>
<td>1.60</td>
<td>1.19–2.15</td>
<td>0.002</td>
</tr>
</tbody>
</table>
increasing QRSd increased more slowly (slope was flatter) among patients with a low EF than a normal EF. However, for any given value of QRSd, the risk of HFH was higher for low-EF patients until very high values of QRSd were reached. When QRSd exceeded \(\approx 200\) ms, the risk of HFH was equivalently increased in low- versus normal-EF patients. The median QRSd was slightly longer among patients with a low versus a normal EF (156 versus 140, \(P=0.001\)).

**MI, QRSd, and HFH Risk**

The shape of the relation between MI, QRSd, and risk of HFH is shown in Figure 3. For any value of QRSd, the relative risk of HFH was always greater among patients with MI. However, unlike the case with EF, there was no significant interaction between MI, QRSd, and HFH risk. This means that the incremental increase in risk of HFH per unit increase in QRSd was the same in MI versus non-MI patients and that the relative risk of HFH by MI versus no MI was constant across the QRSd range. The median QRSd was longer among patients with MI (150 versus 140, \(P=0.001\)), but this difference was probably not clinically significant.

**Predicted 2-Year HFH Rates**

The Cox model was used to generate a predicted probability of HFH by 2 years for typical patients of predefined types and pacing mode/Cum%VP categories (Table 3). Patients with a normal EF, no history of heart failure, and a normal QRSd were at very low risk for HFH, regardless of Cum%VP or pacing mode.

The risk of HFH increased abruptly among patients with a low EF or other evidence of structural heart disease (history of cardiomyopathy or MI), heart failure, advancing NYHA class, and increasing QRSd. The relative risk of HFH was always lower in patients with DDDR/Cum%VP \(\leq 40\) versus DDDR/Cum%VP \(>40\) or VVIR/Cum%VP \(\leq 80\). Patients with a significantly prolonged spontaneous QRSd (\(>140\) ms) were at highest risk for HFH, \(\approx 40\) times higher than in the lowest-risk group.

**Discussion**

This study demonstrates that heart failure during conventional cardiac pacing can be explained by complex interactions between substrate and promoters. Substrate is described by specific physiological and clinical variables, including atrial rhythm, AV conduction, ventricular conduction, ventricular function, and symptomatic heart failure and MI. The promoters of heart failure are specific to the implementation of cardiac pacing and contain 2 constituents: ventricular desynchronization (paced QRSd and Cum%VP) and AV desynchronization (pacing mode).

Patients with a very low-risk substrate (normal EF, no history of heart failure or MI, and normal baseline QRSd) had a correspondingly low risk of HFH that could be attributed to the adverse effects of ventricular desynchronization and AV desynchronization. Although the probability of HFH was \(\approx 2\) times higher in VVIR mode with Cum%VP \(\leq 80\) or DDDR mode with Cum%VP \(>40\) versus DDDR mode with Cum%VP \(\leq 40\), the predicted 2-year probability in either situation was \(<2\%\).

In contrast, patients with a very high-risk substrate (low EF, MI, a history of symptomatic heart failure, and spontaneous pQRSd) had a dramatically increased risk of HFH that
could be attributed to ventricular and AV desynchronization. In this situation, the probability of HFH was increased by nearly 40-fold within each pacing mode/Cum%VP group compared with patients with a low-risk substrate.

Notably, in the extremes of either set of substrate conditions, the lowest relative probability of HFH was consistently observed in patients randomized to DDD/R (AV synchrony) but with a very low Cum%VP (ventricular synchrony), yielding “functional” AAI/R pacing in the context of a dual-chamber pacemaker. This implies that the adverse effects of ventricular and AV desynchronization apply universally during cardiac pacing but are modulated by substrate. For example, the absence of AV conduction and VVIR pacing will result in continuous ventricular and AV desynchronization. Likewise, sinus rhythm, reliable AV conduction, and dual-chamber pacing could potentially yield continuous ventricular and AV synchrony, depending on pacemaker programming and other considerations.

An important question is whether the risk of heart failure increases more quickly with increases in Cum%VP in some patients versus others. We did not observe this. The lack of an interaction between pacing mode/Cum%VP and other predictors of HFH means that the mode/Cum%VP risk effect is additive, rather than multiplicative, and no risk factors predispose a patient to worse outcomes with increasing Cum%VP. However, it is crucial to understand that the equivalence of the Cum%VP-related effect for all patients is in relative rather than absolute risk and so will have a greater impact on patients who have a higher risk of heart failure owing to other factors. The relative risk of HFH is approximately doubled in all patients in the DDD/R mode if Cum%VP is >40 versus a Cum%VP ≤40, regardless of additional risk factors (Table 4). However, although this might only increase the risk from 2% to 4% for patients with few other risk factors, it will increase the risk from 20% to 40% in patients with multiple risk factors, a much larger absolute increase. Thus, patients with multiple risk factors for heart failure will have the same relative increased risk with increasing Cum%VP as do patients with fewer heart failure risk factors but a greater absolute increased risk.

This study also provides, for the first time, strong evidence that the increased relative risk of HFH associated with a more prolonged QRSd is equivalent for prolongation that either occurs spontaneously or is due to RVA pacing (Figure 1). Importantly, the absolute risk of HFH was always ~2-fold higher for a pQRSd that occurred spontaneously versus that due to RVA pacing for any given value of QRSd (Table 2). In distinction to Cum%VP, the increased risk of HFH associated with pQRSd was modified by substrate. The incremental increase in risk of HFH per unit increase in QRSd (spontaneously occurring or due to RVA pacing) was higher in patients with a normal EF, suggesting that these patients were initially more vulnerable to the adverse effects of pQRSd (Figure 2). The chief effect of this interaction was that at the highest values of QRSd (~200 ms), normal- and low-EF patients had equivalent risks of heart failure. Thus, the lower baseline risk of heart failure conferred by a normal versus a low EF was cancelled out when the spontaneous or RVA-paced QRSd was very prolonged. Likewise, patients with a low EF and a pQRSd due to RVA pacing had a nearly equivalent 2-year probability of HFH, regardless of whether baseline QRSd was normal or prolonged (Table 3).

This investigation extends observations from a previous analysis of the MOST population, which demonstrated that paced QRSd was positively correlated with an increased risk of HFH, and this risk increased linearly from lowest to highest values of paced QRSd. This increased risk persisted despite adjustment for other predictors of HFH and was insensitive to pacemaker mode and baseline QRSd. The positive correlation between the magnitude of paced QRSd and risk of HFH is similar to the relation between spontaneously occurring QRSd prolongation and mortality and acute hemodynamic response to cardiac resynchronization therapy in systolic heart failure. The lack of a correlation between baseline QRSd and heart failure in this study may be explained by the observation that RVA pacing resulted in further prolongation of the QRSd, even among patients with a prolonged baseline QRSd.

This study further refines the quantification of ventricular desynchronization burden during RVA pacing. Previously, we demonstrated an increasing risk relation between
Cum%VP and heart failure and that at high levels of Cum%VP, this risk was independent of AV synchronization (pacing mode). The total burden of ventricular desynchronization therefore is a function of the paced QRSd, which is a measure of “potency per dose,” and Cum%VP is the frequency with which the dose is delivered.

The results of this study permit rationalization of clinical experience with conventional cardiac pacing in different patient populations and provide insights for interpreting the results of RCTs of pacing therapy. Most typical pacemaker patients have normal ventricular function, no history of heart failure, and a normal baseline QRSd. These patients tolerate chronic RVA pacing reasonably well and have a low probability of heart failure that can be attributed to pacing therapy (ventricular and AV desynchronization). This likely explains the relative insensitivity of clinical outcomes to Cum%VP and pacing mode in RCTs of pacemaker therapy, regardless of baseline AV conduction status.

On the other hand, although clinical characteristics such as low EF, MI and heart failure, worse functional class, and prolonged baseline QRSd constitute a small portion of patients in RCTs of conventional pacemaker therapy, they define the typical ICD patient population. Whereas in RCTs of pacemaker therapy, in which most patients had (near-) normal systolic function, it took 3 to 5 years before heart failure attributed to RVA pacing became manifest; this period was <1 year in DAVID and MADIT II. Furthermore, this accelerated adverse response to RVA pacing included ventricular arrhythmia and death, in addition to heart failure. Therefore, ventricular desynchronization due to RVA pacing is less tolerated in patients with preexisting systolic heart failure. Our study adds some evidence to this concept by the observations that (1) the effect of pQRSd (paced or spontaneous) on the risk of heart failure was greater among patients with MI or a low EF and (2) the doubling of risk with DDDR Cum%VP >40 or VVIR Cum% VP ≤80 versus DDDR Cum%VP ≤40 was additive with other risk factors for HFH. This underscores the unique value of our study, because it is unlikely that similar data will ever be collected again in an RCT of conventional pacemaker therapy. Patients with an indication for pacemaker therapy who have a low EF and heart failure will likely receive ICDs and depending on QRSd or other measures of ventricular dyssynchrony, cardiac resynchronization therapy.

Study Limitations
The use of retrospective subgroup analysis introduces the possibility that the play of chance influenced the results. Although multivariable analyses control for those characteristics that are recorded based on the study protocol, there remains a chance that the present findings may have been due to uncontrollable differences.

Conclusions
Heart failure during conventional cardiac pacing can be explained by interactions between substrate (atrial rhythm, AV conduction, ventricular conduction, ventricular function) and promoters that relate to the technique of pacing (ventricular desynchronization—paced QRSd and Cum% VP, and AV desynchronization—pacing mode). Management of ventricular pacing is important to reduce the risk of heart failure during cardiac pacing, particularly among patients with reduced ventricular function and heart failure symptoms.

Acknowledgments
The MOST was supported by grants U01 HL 49804 and U01 HL 53973 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Disclosures
Medtronic, Inc, Guidant Corp, and St. Jude Medical donated additional support for study meetings and ancillary studies. Michael O. Sweeney, MD, has received grant support and other research support from, is a paid consultant to, has served on the speakers’ bureau of, and has received honoraria from Medtronic, Inc. Anne Hellkamp reports no disclosures.

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Right ventricular apical (RVA) pacing alters the left ventricular (LV) electrical activation sequence, resembling left bundle-branch block. The resulting electrical asynchrony is manifest in prolonged QRS durations due to slow myocardial conduction. Consequently, LV contraction is disturbed and ventricular dyssynchrony may occur. Ventricular desynchronization imposed by RVA pacing results in reduced pump function, mitral regurgitation, increased left atrial diameter, hypertrophy, and ultrastructural abnormalities. These adverse effects of RVA pacing on cardiac structure and function are common to all ventricular pacing modes and are independent of atrioventricular (AV) synchrony during cardiac pacing. PACing-induced ventricular desynchronization has been linked to an increased risk of atrial fibrillation, heart failure, ventricular arrhythmias, and death in pacemaker and implantable cardioverter-defibrillator trials. These adverse effects are accelerated in the presence of systolic heart failure. Manipulation of pacing modes and timing cycle operation among patients with reliable AV conduction is necessary to minimize potentially harmful ventricular pacing and maximally preserve intrinsic ventricular activation and contraction patterns. An atrially based dual-chamber minimal ventricular pacing strategy is recommended to prevent symptomatic bradyarrhythmias during paroxysmal AV block or atrial fibrillation. This strategy should serve the vast majority of patients treated with pacemakers for sinus node dysfunction or intermittently AV block and many patients who are candidates for implantable cardioverter-defibrillator therapy. Efforts to minimize RVA pacing should be greater in patients with a longer expected duration of pacing, poorer cardiac function, and larger hypertrophy, and ultrastructural abnormalities. These adverse effects of RVA pacing on cardiac structure and function are common to all ventricular pacing modes and are independent of atrioventricular (AV) synchrony during cardiac pacing. PACing-induced ventricular desynchronization has been linked to an increased risk of atrial fibrillation, heart failure, ventricular arrhythmias, and death in pacemaker and implantable cardioverter-defibrillator trials. These adverse effects are accelerated in the presence of systolic heart failure. Manipulation of pacing modes and timing cycle operation among patients with reliable AV conduction is necessary to minimize potentially harmful ventricular pacing and maximally preserve intrinsic ventricular activation and contraction patterns. An atrially based dual-chamber minimal ventricular pacing strategy is recommended to prevent symptomatic bradyarrhythmias during paroxysmal AV block or atrial fibrillation. This strategy should serve the vast majority of patients treated with pacemakers for sinus node dysfunction or intermittently AV block and many patients who are candidates for implantable cardioverter-defibrillator therapy. Efforts to minimize RVA pacing should be greater in patients with a longer expected duration of pacing, poorer cardiac function, and larger mechanical asynchrony. Awareness of the problem of desynchronization should sponsor regular monitoring of cardiac pump function and mechanical asynchrony in any patient with ventricular pacing.