Heart Failure Decompensation and All-Cause Mortality in Relation to Percent Biventricular Pacing in Patients With Heart Failure

Is a Goal of 100% Biventricular Pacing Necessary?

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Objectives
The goal of this analysis was to determine the appropriate biventricular pacing target in patients with heart failure (HF).

Background
Cardiac resynchronization therapy (CRT) decreases the risk of death and HF hospitalization. However, the appropriate amount of biventricular pacing is ill-defined.

Methods
Mortality and HF hospitalization data from patients undergoing CRT in 2 trials (CRT RENEWAL [Cardiac Resynchronization Therapy Registry Evaluating Patient Response with RENEWAL Family Devices] and REFLEX [ENDOTAK RELIANCE & Evaluation of Handling and Electrical Performance Study]; n = 1,812) were analyzed in a post-hoc fashion. Subjects were grouped based on percent biventricular pacing quartiles with the use of Kaplan-Meier survival analysis.

Results
Subjects were age 72 ± 11 years; 72% were men and 67% had coronary artery disease. Subjects paced 93% to 100% (quartiles 2 to 4) had a 44% reduction in hazard of an event compared with subjects paced 0% to 92% (quartile 1; hazard ratio [HR]: 0.56, p < 0.0001). Subjects paced 98% to 99% (quartile 3) had similar outcomes as subjects paced 93% to 97% (quartile 2; HR: 0.97, p = 0.82). Subjects paced 100% (quartile 4) had similar outcomes as subjects paced 98% to 99% (HR: 0.78, p = 0.17). There was a significant interaction between a history of atrial arrhythmia and percent pacing. Subjects with a history of atrial arrhythmia were more likely to be paced <92% (p < 0.001).

Conclusions
For CRT patients in this retrospective analysis, the greatest magnitude of benefit was observed with >92% biventricular pacing. (J Am Coll Cardiol 2009;53:355–60) © 2009 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure (HF) decompensation and hospitalization rates and to improve exercise tolerance and left ventricular remodeling in subjects with moderate or severe symptomatic HF and evidence of dyssynchrony (1–6). It is generally believed that near-maximal biventricular pacing is necessary to assure optimal CRT response. One study used an arbitrary cutoff rate of biventricular pacing >85% of pacing time (7). However, the appropriate target for biventricular pacing percentage is ill-defined. In some patients with brisk atrioventricular nodal conduction either in sinus rhythm or while in atrial fibrillation (AF), 100% pacing can be challenging to achieve. This challenge is important, because AF frequently is associated with HF (8) and has been shown to be an independent predictor of morbidity and mortality (9,10). Whether incremental benefit occurs beyond a pacing percentage of 85%, 90%, or greater is uncertain. We sought to determine whether or not incremental benefit in mortality and HF hospitalization occurs with pacing at or near 100% compared with lower pacing percentage rates in a large cohort of patients.
Methods

Subjects. All-cause mortality and HF hospitalization data from 1,812 subjects undergoing CRT in 2 trials, the CRT RENEWAL (Cardiac Resynchronization Therapy Registry Evaluating Patient Response with RENEWAL Family Devices) (11) and REFLEx (ENDOTAK RELIANCE G Evaluation of Handling and Electrical Performance) (12), were analyzed in a post-hoc fashion. Subjects enrolled in the 2 trials met current device indications and were implanted with a CRT defibrillator. Subjects were followed up at implant, wound check, and 3, 6, and 12 months after implant.

At each follow-up visit, subjects were asked whether they had been seen for an HF hospitalization since their last visit and the date of this event. To be considered an HF hospitalization, a subject must have been hospitalized for >24 h with worsening of symptoms and had 1 or more intensive treatments (intravenous [IV] diuretics, IV nesiritide, IV inotropes, placement on transplant list) for HF. Device interrogation also was performed at each visit.

Statistical analyses. Subjects were grouped based on lifetime biventricular pacing percentages (total paced left ventricular beats divided by total paced + sensed beats over the lifetime of the device) with the use of Kaplan-Meier survival analysis with a combined end point of HF hospitalization and all-cause mortality. Baseline demographics were evaluated using summary statistics. The Cochrane-Armitage test for trend in proportions was used to evaluate a trend in the event rate (events per follow-up month) with increased biventricular pacing. Multivariate Cox proportional hazards survival models also were used to evaluate lifetime biventricular pacing adjusting for a number of baseline clinical and demographic factors as a predictor of the time to the combined end point. A p value <0.05 was considered statistically significant without adjustment for multiple comparisons. These analyses were performed using the R statistical software package version 2.5.1 (13).

A secondary analysis also was performed with the recent percent time in atrial tachycardia response (ATR) mode switch and recent percent biventricular pacing values collected at in-clinic visits throughout follow-up as predictors of the time to the combined end point event. For this analysis, we fitted a Cox proportional hazards survival model with these variables as time-dependent covariates, while continuing to adjust for baseline predictors as fixed covariates. This analysis was conducted to address concern over potential discrepancies between the lifetime pacing percent for the patient and pacing in the time interval during which an event occurred, as well as the potential impact of the development of AF (as indicated by the ATR mode switch percent) over the course of follow up. This analysis was performed using SAS statistical software version 9.1 (SAS Institute, Cary, North Carolina).

Results

Demographics. Subjects enrolled in the 2 studies were typical of the HF population enrolled in large clinical trials: a high percentage of men, most with New York Heart Association (NYHA) functional class III HF, a majority with a history of coronary artery disease, and approximately 35% with a history of atrial arrhythmia (included a history of atrial fibrillation, atrial flutter, atrial tachycardia) (Table 1). This history of atrial arrhythmia was based on answers to a questionnaire in both studies. Median follow-up was 10.7 months.

Outcomes. Figure 1 illustrates the number of subjects that were biventricularly paced at each percentage. A multivari-
ate Cox model was used to identify predictors of death or HF hospitalization (Table 2). A history of diabetes (hazard ratio [HR]: 1.43, p = 0.002), coronary artery disease (HR: 1.55, p = 0.002), and atrial arrhythmia (HR: 1.34, p = 0.001), and worse NYHA functional class (II vs. III, HR: 0.66, p = 0.042; III vs. IV, HR: 0.55, p < 0.001) had a greater hazard of experiencing death or HF hospitalization. Because data were combined from 2 studies, after adjusting for covariates, the study was put into the Cox proportional hazards survival model and was found to not be a predictor of HF hospitalization and all-cause mortality (p = 0.35).

Subjects were divided into quartiles based on percent biventricular pacing (Fig. 2): Quartile (Q)1 = 0% to 92% (n = 467), Q2 = 93% to 97% (n = 474), Q3 = 98% to 99% (n = 509), and Q4 = 100% (n = 362). Subjects paced in Q2 to Q4 had a 44% reduction in hazard of an event compared with subjects paced in Q1 (HR: 0.56, p < 0.00001). Subjects paced in Q2 had a 38% reduction in hazard of an event compared to subjects paced in Q1 (HR: 0.62, p = 0.0013). Subjects paced in Q3 had similar outcomes as subjects paced in Q2 (HR: 0.97, p = 0.82). Subjects paced in Q4 had similar outcomes as subjects paced Q3 (HR: 0.78, p = 0.17). The test for trend for fewer events as pacing increased was highly significant (p < 0.00001).

Subjects paced in Q1 were more likely to be men (p = 0.006) and have a history of atrial arrhythmia (p < 0.001). However, patients paced in Q1 were less likely to have a history of diabetes (p = 0.008) or hypertension (p = 0.01) (Table 3).

On the basis of the likelihood ratio test, it was determined that a history of atrial arrhythmia had a significant interaction with pacing percentage. Therefore, the interaction term was included, modeling the impact of pacing for subjects with a history of atrial arrhythmia and subjects without a history of atrial arrhythmia separately.

**Subjects with no history of atrial arrhythmia.** In subjects with no history of atrial arrhythmia (Fig. 3A), the model demonstrates incremental benefit in the combined end point with increasing levels of pacing percentage, even with greater pacing percentages. Subjects paced in Q2 to Q4 (93% to 100%) had a 32% reduction in hazard of an event compared with subjects paced in Q1 (0% to 92%; HR: 0.68, p = 0.02). Subjects paced in Q3 to Q4 (98% to 100%) had a 34% reduction in hazard of an event compared with subjects paced in Q2 (93% to 97%; HR: 0.66, p = 0.01). And, subjects paced in Q4 (100%) had a 34% reduction in hazard of an event compared to subjects paced in Q2 to Q3 (93% to 99%; HR: 0.66, p = 0.04). The test for trend for fewer events as pacing increased was also significant (p = 0.002).

**Subjects with a history of atrial arrhythmia.** In subjects with a history of atrial arrhythmia (Fig. 3B), subjects paced Q2 to Q4 (93% to 100%) had a 56% reduction in hazard of an event compared with subjects paced in Q1 (0% to 92%; HR: 0.44, p < 0.00001). Subjects paced in Q2 had a 65% reduction in hazard of an event compared with subjects paced in Q1 (HR: 0.35, p < 0.001). Beyond this, however, there did not appear to be incremental benefit as percent pacing increased with regard to the combined end point. The test for trend for fewer events as pacing increased was significant (p = 0.002).

**Subjects with atrial arrhythmia during follow-up.** Because of the interaction between history of atrial arrhythmia and pacing percentage, the actual time spent in ATR mode switch (as a proxy for time spent in AF) was evaluated. The 95th percentile for ATR mode switch percentage was 9%. There were 138 (7.6%) patients that had lifetime ATR mode switch percent (as measured at the last follow-up visit for the lifetime of the device) >9%. Mode switch percentages, as well as biventricular pacing percentages, also were examined at each in-clinic visit (recent ATR mode switch, recent biventricular pacing percentage). One hundred seventy-six (9.7%) patients had a recent ATR mode switch >9%. Recent ATR mode switch percentage >9% was not a predictor of the combined end point of HF hospitalization and all-cause mortality after adjusting for baseline covariates.
in a Cox model analysis with time-dependent covariates (14). However, patients with a lifetime ATR mode switch percentage >9% were at increased risk of HF hospitalization or all-cause mortality compared with subjects with lifetime ATR mode switch ≤9% (HR: 1.51, p = 0.018). After adjusting for baseline covariates, including history of atrial arrhythmia, as well as lifetime and recent biventricular pacing percentage, lifetime ATR mode switch >9% was no longer significant. Interestingly, both recent (HR: 1.406, p = 0.01) and lifetime biventricular pacing percentages ≥92% (HR: 1.424, p = 0.0087) were significant and remained significant even when both were included in a multivariate model adjusting for baseline covariates and lifetime ATR mode switch dichotomized at 9%.

We also examined recent and lifetime ATR mode switch >0%. There were 261 (14.4%) patients with lifetime ATR mode switch >0% and 376 (20.8%) patients with recent ATR mode switch >0%. Similar to the results in patients with ATR mode switch ≥9%, only lifetime ATR mode switch was associated with the combined end point of HF hospitalization and all-cause mortality (HR: 1.32, p = 0.05).

**Why some subjects do not pace >92%**. Subjects paced ≤92% had more LV lead-related adverse events (p = 0.001), were more likely to have a history of atrial arrhythmia (p < 0.001), and were less likely to have device algorithms to increase ventricular pacing percentage during atrial arrhythmias, such as ventricular rate regulation (VRR), programmed on (p < 0.001). Subjects with lower percent pacing also had a greater programmed mean fixed atrioventricular (AV) delay (p < 0.001) and a greater mean maximum (p = 0.003) and minimum (p = 0.001) dynamic AV delay than subjects that were paced >92% of the time (Table 4). After adjusting for baseline covariates and lifetime biventricular pacing quartile, programming mode did not have an impact on whether patients were paced >92%. Of the 1,812 patients, 1,387 (77%) were programmed DDD and 172 (9%) were programmed VVI at all follow-up visits. The remaining 14% of patients did not have a consistently programmed mode throughout follow-up, but it was limited to DDD, VVI, DDI, or VDD.

**Table 3** Baseline Covariates for Patients Paced ≤92% Versus Patients Paced >92%

<table>
<thead>
<tr>
<th></th>
<th>Q1 (0% to 92% (n = 467)</th>
<th>Q2 (93% to 97% (n = 474)</th>
<th>Q3 (98% to 99% (n = 509)</th>
<th>Q4 (100% (n = 362)</th>
<th>p Value for Q1 vs. Q2 to Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (% male)</td>
<td>359 (76.9)</td>
<td>344 (72.6)</td>
<td>365 (71.1)</td>
<td>230 (63.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes</td>
<td>124 (26.6)</td>
<td>157 (33.1)</td>
<td>178 (35.0)</td>
<td>111 (30.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>History of CAD</td>
<td>298 (63.8)</td>
<td>339 (71.5)</td>
<td>354 (69.6)</td>
<td>219 (60.5)</td>
<td>0.114</td>
</tr>
<tr>
<td>History of atrial arrhythmia</td>
<td>200 (42.8)</td>
<td>161 (34.0)</td>
<td>148 (29.1)</td>
<td>108 (29.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>210 (45.0)</td>
<td>255 (53.8)</td>
<td>258 (50.7)</td>
<td>157 (43.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>247 (52.9)</td>
<td>281 (59.3)</td>
<td>318 (62.5)</td>
<td>204 (56.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>60 (12.9)</td>
<td>55 (11.6)</td>
<td>52 (10.2)</td>
<td>43 (11.9)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>348 (74.5)</td>
<td>374 (78.9)</td>
<td>388 (76.2)</td>
<td>280 (77.4)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>34 (7.3)</td>
<td>35 (7.4)</td>
<td>64 (12.6)</td>
<td>30 (8.3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise specified.

CAD = coronary artery disease; NYHA = New York Heart Association; Q = quartile.
Interestingly, 54% of patients paced >92% improved by at least 1 NYHA functional class between implant and 6 months, whereas 46% of patients paced ≤92% improved by at least 1 NYHA functional class (p = 0.014).

### Discussion

This large retrospective analysis is the first to investigate appropriate biventricular pacing percentage in patients with HF receiving CRT. In our analysis of >1,800 patients, the greatest magnitude of reduction in HF hospitalization and all-cause mortality was observed with a biventricular pacing cutoff of 92%. It is interesting that in our analysis, the patients paced ≤92% had worse outcomes and were less likely to improve 1 NYHA functional class from implant to 6 months than patients paced >92%. Previous studies have shown that approximately 30% of patients treated with CRT do not respond to treatment (4,15).

Because AF is often associated with HF and is an independent risk factor for morbidity and mortality (9,10) and because AF can reduce the percentage of ventricular pacing, we examined the effect that a history of atrial arrhythmia at implant had on the outcome of mortality and HF hospitalization. It is widely perceived that the combination of AF and HF results in a worse prognosis than either by itself. And, indeed, we did find a significant interaction between a history atrial arrhythmia at implant and percent biventricular pacing with respect to the combined end point of all-cause mortality and HF hospitalization in this retrospective analysis. In patients with no history of atrial arrhythmia, a greater pacing percentage (98% or greater) showed a significant incremental reduction in mortality and HF hospitalization compared with pacing 93% to 97%. However, for patients with a history of atrial arrhythmia, pacing incrementally >92% (i.e., 98% to 99% vs. 93% to 97% and 100% vs. 98% to 99%) did not further reduce the risk of HF hospitalization and all-cause mortality.

Because the occurrence of AF is an independent predictor of morbidity and mortality (9,10), we also examined the percentage of time a subject spent in ATR mode switch because pacemakers often are programmed to mode-switch in the presence of atrial arrhythmias (16). Interestingly, subjects with lifetime ATR mode switch (as measured at final follow-up visit) >9% or >0% were at increased risk of all-cause mortality or HF hospitalization, but ATR mode switch >9% or >0% measured at the most recent follow-up visit was not associated with worse outcomes. These data are similar to those recently reported by Gilliam et al. (17), who found that patients with chronic high-rate atrial arrhythmia burden (possible marker for AF) have a greater incidence of HF decompensation but that high-rate atrial burden does not necessarily increase prior to HF decompensation. Our analyses clearly indicate that AF occurrence alone does not account for the increased risk of HF hospitalization and all-cause mortality associated with lower biventricular pacing percentages.

To address the concern of collecting the predictor (biventricular pacing percentage) after the outcome (HF hospitalization or all-cause mortality), we examined biventricular pacing percentage at each follow-up visit (recent biventricular pacing percentage). Unlike ATR mode switch, where recent ATR mode switch was not a predictor of HF hospitalization or all-cause mortality, recent biventricular pacing percentages ≤92% were significant predictors of the combined end point, again highlighting the implication that lower biventricular pacing percentages result in worse outcomes, which also may be a clinical concern if a patient’s biventricular pacing percentage suddenly decreases.

Although it would seem practical to program devices to achieve maximal percent pacing when CRT therapy is provided, our findings have certain clinical implications. For patients in whom 100% pacing is not easily achieved because of enhanced AV nodal conduction either in sinus rhythm or while in atrial fibrillation, our analysis provides guidance regarding a reasonable goal to try to attain. Our results could also provide appropriate desired percent pacing cutoffs for future research.

### Implications for increasing biventricular pacing

We found a statistically lower utilization rate of the VRR algorithm in patients with 0% to 92% pacing compared with patients paced 93% to 100%, suggesting that a more aggressive use of the VRR algorithm could increase the percent biventricular pacing in patients that experience atrial arrhythmias. In addition, lowering AV delays also increases the percentage of biventricular pacing.
Study limitations. The limitations of our analysis include that it was a retrospective cohort analysis. Although we accounted for important covariates, like atrial fibrillation, we cannot conclusively determine the independent effects of AF and biventricular pacing percentage. In addition, the exact time-course of changes in pacing percentage, occurrence of AF and their relationship to an event was not evaluated. Finally, confounders to pacing counters like fusion/pseudofusion could not be assessed because the information required was not collected in these 2 studies. Larger prospective studies are required to confirm our findings.

Conclusions

For patients undergoing CRT in this retrospective analysis, the greatest magnitude of benefit was observed with >92% biventricular pacing. Although percent biventricular pacing should be maximized whenever possible, the data in this retrospective analysis provide guidance with respect to the percent pacing that should be targeted in patients whom 100% biventricular pacing is difficult to achieve.

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REFERENCES


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