Cardiac resynchronization therapy (CRT) has been shown to improve quality-of-life, functional status, exercise capacity, and survival in patients with left ventricular systolic dysfunction, moderate to severe heart failure symptoms, and a wide QRS.1–4 Controlled, randomized CRT trials have used atrial sensing to provide atrial-synchronized biventricular pacing, but have not focused on atrial pacing or rate response. Current CRT devices are capable of atrial pacing for atrial rate support and rate-responsive pacing (DDDR), and these are 2 commonly programmed modes in CRT devices. However, no randomized prospective clinical trial has shown survival benefit from these pacing modes.

Increasing heart rate through atrial support pacing in heart failure patients can increase cardiac output. However, higher resting and mean heart rates are associated with increased mortality.5,6 In a heart failure population, although lower resting rates are associated with better outcomes, no one has specifically considered outcomes in those with lower resting heart rates but better heart rate response with exercise. Similarly, in an implantable cardioverter defibrillator (ICD) population, the mean heart rate predicts outcomes of heart failure hospitalization and total mortality, but this generally represents resting rate and does not provide information about heart rate changes with exertion or in other circumstances. Chronotropic incompetence, either pathophysiologic or iatrogenic (eg, β-blocker therapy), is common in heart failure patients. In these patients, it is reasonable to suspect that the hemodynamic benefits of biventricular pacing may be enhanced by increasing atrial rates with increased physical demands.

Large, remote monitoring databases offer the opportunity to assess associations between programming parameters and clinical outcomes. A novel parameter, the heart rate score (HRSc),
Heart Rate Score Is Associated With Survival

Olshansky et al

may help distinguish which patients are in need of DDDR pacing. A high HRSc (≥70%) has been associated with both chronotropic incompetence and increased mortality.7,8 We hypothesized that CRT defibrillator (CRT-D) patients with a HRSc ≥70% identified via remote monitoring would have improved survival with DDDR versus nonrate-responsive (DDD) pacing.

WHAT THE STUDY ADDS

- The Heart Rate Score, a measure of chronotropic incompetence, identified CRT-D patients who have improved survival with rate-responsive (DDDR) pacing.
- Rate-responsive pacing improves survival in patients with chronotropic incompetence.

Methods

HRSc was defined as the percent of all paced and sensed atrial events in the single tallest 10 beats per minute rate histogram bin (Figure 1). A HRSc of 100% requires that all paced and sensed beats occur in the same histogram bin. Lower HRScs occur when atrial events are distributed over a range of rates. Therefore, the HRSc is a geometric measure of heart rate recorded by device histograms. It is related to the long-term variation of heart rate (Figure 1). The first observations that led to the development of the concept of the HRSc originated from the LIFE trial (Limiting Chronotropic Incompetence for Pacemaker Recipients), in which chronotropic incompetence was associated with a HRSc ≥70%.7 Following this, a prospective analysis (unpublished) revealed that survival in patients with ICDs or CRT-Ds was decreased in those with higher HRSc scores.8

Patients included in this study underwent implantation of dual-chamber Boston Scientific Corporation CRT-Ds and were monitored remotely via the LATITUDE remote monitoring system from 2006 to 2011. The data were part of the ALTITUDE study database, which is a deidentified database whose use has been approved by the Boston Scientific governance board. No individual patients were studied, and, therefore, no institutional review board approval was necessary. Patients programmed DDD as an initial setting had a HRSc calculated at the time of the first LATITUDE upload. The baseline HRSc was determined from the first data upload post device implant. HRScs were divided into 3 groups: <30%, 30% to 69%, and ≥70% for simplicity, but were also considered as a continuous variable (unpublished) and in deciles.8 The rationale for the 3 HRSc groups was based on the LIFE study analysis, with only HRSc group ≥70% having a reduction in HRSc with DDDR pacing.2 Deaths as reported through the manufacturer’s device tracking system and through the Social Security Death Index.

Study Cohort

All patients programmed to the DDD mode at time of initial data upload were included (Figure 2). Devices implanted before US market release of the LATITUDE system in 2006 were excluded. Patients with a baseline HRSc, defined by a histogram rate bin above 170 beats per minute, were excluded. That is, patients were excluded if the tallest histogram bin occurred at a rate above the nominal setting for atrial tachycardia response mode switch, likely indicating persistent or chronic atrial fibrillation. Patients with programming changes to the lower rate limit parameter during follow-up were excluded (Figure 2) because this parameter has been shown to be independently associated with survival.

Patients initially programmed to DDD mode and reprogrammed to DDDR mode during follow-up were propensity score–matched to patients who remained in DDD mode throughout follow-up. For purposes of the match and subsequent analyses, a transition date was determined for each patient. For patients reprogrammed to DDDR, the date of transition was defined as the date of reprogramming to DDDR. For patients remaining in DDD throughout follow-up, the date of transition was defined as the average date of reprogramming in the DDDR group: 15 months post implant. The HRSc at the date of transition was defined as the baseline HRSc.

On average, baseline HRScs were calculated using >160000000 beats, with 96% of patients having their baseline HRScs calculated with at least 10000000 beats. DDDR patients were matched 1:1 to DDD patients by baseline HRSc, age, sex, implant year, biventricular

WHAT IS KNOWN

- Rate-responsive pacing has been utilized in various clinical circumstances, even though randomized clinical trials do not show benefit.
- Chronotropic incompetence can occur in patients with cardiac resynchronization therapy defibrillators (CRT-D), and its presence may identify a population at greater risk of dying.
Heart Rate Score Is Associated With Survival

Statistical Analysis

Demographics for the DDDR and DDD groups were compared using standardized difference scores. A Kaplan–Meier survival curves were constructed for baseline HRSc group (<30%, 30% to 69%, and ≥70%). Stratified log-rank tests were performed to compare patients initially programmed to DDDR mode to those reprogrammed to DDDR mode during follow-up. Stratification by propensity score quintile was used because it cannot be assumed that the DDDR and DDD groups are independent. Time to event was analyzed from date of transition (ie, DDDR programming date for DDDR group and at 15-month postimplant date for each DDD match). Multivariate Cox proportional hazards models were performed adjusted for age, sex, lower rate limit, percent atrial pacing, percent biventricular pacing, and implant year. To account for the matched nature of the sample, each Cox model was stratified by propensity score and a robust sandwich variance estimator. Change in HRSc was assessed for each baseline HRSc group using a paired t test, with each pair consisting of a DDDR patient and a DDD patient. The paired t test was used because it cannot be assumed that the DDDR and DDD groups are independent. Programming of the lower rate limit was constant during the baseline period. Follow-up was considered through December 31, 2012, to allow for a lag in reporting of deaths.

Results

The entire ALTITUDE CRT-D population included 42,894 patients. After excluding patients who had devices implanted before 2006 (N=47,48), those who had a predominant HRSc >170 beats per minute likely because of chronic atrial fibrillation (N=16,78), and those with inconsistent lower rate limit programming between implant and the transition date (N=1,838), the propensity-matched study cohort included 6164 patients. There were 3082 patients consistently programmed to DDD throughout follow-up and 3082 reprogrammed from DDD to DDDR during follow-up (Figure 2). The median time from implant to first LATITUDE upload was 1.4 (interquartile range 0.7–3.2) months, and the median time from implant to DDDR reprogramming was 7.6 (interquartile range 3.4–17.2) months. The median follow-up time after the transition date was 21.4 (interquartile range 9.6–36.8) months, and the total follow-up time included 12,119 patient-years. Baseline demographics are shown in Table. Age was associated with the HRSc, and the majority of patients in the matched cohort had a baseline HRSc of 30% to 69%. However, 37% had a HRSc ≥70%.

In the propensity-matched DDD group, follow-up times were comparable to those of the DDDR group (DDDR, 2.0 years; DDD, 1.9 years). Over time, the mean HRSc for all patients in each group was nearly constant (DDDR, 1.0% decrease; DDD, 0.5% increase). However, when analyzed by 10% increments in HRSc, there were clear differences in the influence of DDDR programming on HRSc (Figure 3). In patients with baseline HRSc ≥70%, DDDR pacing decreased HRSc significantly (Figure 4). The most substantial decrease occurred in the 91% to 100% group (>13% decrease in HRSc Figure 3), but it was present throughout the HRSc ≥70% group (a 10% decrease in HRSc for the ≥70% group). For the other 2 HRSc groups, 30% to 69% and <30% DDDR programming actually led to modest increases in the HRSc group (Figure 4; P<0.001 for each group).

Time-to-event analyses, comparing propensity-matched groups based on the baseline HRSc, showed that only patients with a baseline HRSc ≥70% had survival benefit with DDDR programming (Figures 5A and 6; hazard ratio =0.74; 95% confidence interval 0.63–0.87; P<0.001). The HRSc 30% to 69% group (Figures 5B and 6) also showed minor nonsignificant survival effect with DDDR pacing (hazard ratio =0.90, 95% confidence interval 0.78, 1.02; P=0.106). The lowest HRSc group (<30%) showed no survival benefit with DDDR programming (P=0.403; Figures 5C and 6).

We considered the relationship between HRSc improvement and survival by patient rather than population. There was a tight relationship between HRSc improvement and outcomes in patients reprogrammed to DDDR with baseline HRSc ≥70% (hazard ratio =0.63; P=0.006). Furthermore, in the group with HRSc ≥70%, despite reduction in their HRSc,
the mean HRSc after DDDR programming was still high at 78%, reflecting the possibility for even more improvement with optimization of rate response. The changes in HRSc in individual patients varied from a decrease of 69% to an increase of 25%. In 28% of patients, the HRSc transitioned to a lower risk zone of <70% after DDDR programming.

The HRSc increased for those programed DDDR with a baseline HRSc <70% but decreased for those with a HRSc ≥70%. Although statistical regression to the mean is a remote possibility, this is unlikely in such a large population followed long term for the following reasons: the differences were highly statistically significant, and, yet, the baseline measurements were stable and were made over a long period of time with many beats recorded. It would, therefore, be highly unusual, but not totally inconceivable, that further HRSc measurements would show a fluctuation, and regression to the mean only with rate response turned on and, for the group with higher HRSc, that, with rate response turned on, HRS would drop. Additionally, there were small changes in a matched group continuing as DDD programming (Figure 3). Therefore, majority of the change in HRSc does not seem consistent with regression to the mean.

We evaluated percent biventricular pacing in both groups and found that programming rate response on did not affect the percent RV/LV pacing in the DDDR versus DDD group (Table). Thus, it was unlikely that changes in biventricular pacing affected outcomes. We considered the lower rate limit in both groups and found that there were no significant differences in lower rate limit values in the DDD and DDDR groups.

**Discussion**

We show, for the first time, that rate-responsive dual-chamber (DDDR) programming in CRT-D patients is associated with significant improvement in survival but only for a select high-risk population identified by a novel parameter, the HRSc.
Prior Clinical Trials Examining Outcomes in Relationship to Pacing Modes

An assessment of potential benefit of DDDR logically is confined to those pacemaker patients who have chronotropic incompetence (ie, sick sinus syndrome). Unfortunately, no gold standard determines exactly what chronotropic incompetence is, and no tool has been developed yet to determine who will improve with rate-response programming. When considering outcomes of pacing in sick sinus syndrome, 10 retrospective studies showed a 50% reduction in mortality with dual-chamber versus single-chamber pacing.14

The Danish trial of Anderson et al stands out as the only randomized controlled clinical trial showing a significant reduction in mortality, albeit at a study duration longer than the predetermined period.15 This study is remarkable because all 225 patients had sinus node dysfunction and were randomized to atrial or ventricular pacing. Unnecessary right ventricular pacing was essentially eliminated in the atrial pacing group, whereas there was significant ventricular pacing in the VVIR (single-chamber, ventricular-paced, rate-responsive) group. The difference in unnecessary right ventricular pacing likely affected mortality differences. Furthermore, because all patients received rate response, this study cannot assess the value of rate response.

The INTRINSIC RV trial (Inhibition of Unnecessary RV Pacing With A V Search Hysteresis in ICDs) compared DDDR-60–130 to VVI-40 (essentially intrinsic rate), with little unnecessary

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AF indicates atrial fibrillation; DDD, nonrate-responsive pacing; DDDR, rate-responsive pacing; HR, heart rate; HRSc, heart rate score; IQR, interquartile range; and LV, left ventricle.

*Standardized Difference=difference in means or proportions divided by standard error. Imbalance defined as absolute value >0.20 (small imbalance, 0.2–0.49; medium imbalance, 0.5–0.79; large imbalance, ≥0.8).
right ventricular pacing in an ICD population not targeted to have chronotropic incompetence. It showed a trend toward survival benefit with DDDR pacing. The PEGASUS trial (Pacing Evaluation—Atrial Support Study in Cardiac Resynchronization Therapy) found no benefit of atrial support pacing or rate-responsive pacing versus DDD-40 pacing in patients with CRT-D implants. In fact, no randomized prospective trial concluded that DDDR reduces mortality. However, appropriate patient selection may determine who benefits and who does not.

**Potential Reasons Why Prior Trials Did Not Show Benefit With DDDR**

No prior randomized, controlled, clinical trial has focused specifically on DDDR in the CRT-D population. Potential problems
with the prior large, randomized, controlled, clinical trials that have attempted to evaluate outcomes based on programming and device characteristics regarding atrial-based and DDDR include that they have not been able to factor out the impact of right ventricular pacing (DAVID I [The Dual Chamber and VVI Implantable Defibrillation]) or have only considered nonrate-response atrial pacing (DAVID II). Unopposed right ventricular pacing that had potentially confounded the analysis of some prior trials (DAVID I) was not an issue in our study because all patients had a high degree of biventricular pacing (Table). Further, no study has yet considered targeting a high-risk heart failure group with chronotropic incompetence, in whom there is little heart rate variation and for whom DDDR may help.

Too fast a heart rate could have an adverse effect. Based on results from the INTRINSIC-RV Trial, higher mean heart rates were associated with adverse outcomes in patients undergoing ICD implant. However, transient increases in heart rate from a lower baseline resting rate, as needed, were not evaluated and, based on our results shown here, may be beneficial. For others, such as patients with robust spontaneous heart rate variation and low HRScs, additional, and unnecessary, DDDR may have adverse effects.

Possible Mechanisms Explaining Reduced Mortality With DDDR Pacing and Decreased HRSc
Chronotropic incompetence has been shown to be highly prevalent in the heart failure population with reduced ejection fraction, with numbers ranging from 25% to 70%, using conventional definitions of reductions in rate response reserve. However, its contribution to cardiovascular morbidity and mortality remain underappreciated, likely because of limitations in identification of chronotropic incompetence and of the fundamental responsible mechanisms.

Recent elegant work by Benes et al has dissected out chronotropic incompetence into a resting heart rate and heart rate reserve components in a small cohort of CRT-D patients. Fully two thirds of their patients displayed chronotropic incompetence. A combined outcome of death, transplantation, or urgent assist device was associated with less heart rate reserve, a measure of chronotropic incompetence. Resting heart rate and heart rate reserve were not correlated with each other and were associated with distinct biomarker profiles. Both higher resting heart rate and lower heart rate reserve identified patients more likely to die or require transplantation.

Along these lines, the HRSc might identify patients with low heart rate reserve who might benefit from DDDR. This is particularly attractive because both the method and the intervention to improve mortality are achieved easily. This merits further study in a prospective fashion. Likewise, a more physiological sensor, such as minute ventilation, may produce the greatest clinical benefit in high HRSc patient and needs to be evaluated.

At best, however, our hypothesis can only be tested in a trial of high-risk heart failure patients with chronotropic incompetence in which patients are randomized to DDD or DDDR pacing modes with follow-up data collected prospectively in a blinded fashion. From these present data, HRSc may predict benefit from DDDR pacing, realizing that benefit has many meanings, including survival, exercise tolerance, and improved symptoms not measured here.

Limitations
These data were from a post hoc (retrospective) analysis of data that were not collected in a manner that allows testing of the central hypothesis that patients with chronotropic incompetence have improved survival, which is causally related to rate-adaptive pacing. The results are associations observed in large populations. The database does not contain patient symptoms or quality-of-life, and, thus, they are not assessed.

Because the data were propensity-matched based on select criteria, perhaps not all the necessary criteria were selected. However, one would suspect that patients programmed DDDR may be a high-risk population because of specific symptoms, leading to the need for rate-response programming, and yet, outcomes improved at least in the highest risk group. On the contrary, this group programmed DDDR may be a more motivated group who were expecting a greater response from their implanted device, and, therefore, they strove to derive all the benefits they could, and, perhaps, they were a healthier lot. Other trials using propensity-matched analyses have the same conundrum. We did not expect to address all issues regarding why, or if, programming based on HRSc is the cause for improved outcomes; this is just a first step.

We do not know the shortest length of time necessary to get the most robust and reproducible HRSc. The relationships between rate-response programming characteristics and outcomes in individual patients may be more challenging to obtain than in a prospective trial. The mechanism of death is uncertain in those who have high HRScs. The best method to program,
and how to program, rate response (minute ventilation or accelerometer) is unknown. Medication details remain uncertain.

Several questions remain unanswered: Were doctors who reprogrammed devices more adept at pacing management? Were patients remaining with DDD programming felt to be less likely to benefit from rate-adaptive pacing? Did patients more demanding of improved effort tolerance, thereby prompting their physicians to activate the DDDR mode? Could reprogramming to the DDDR mode simply have selected a group fated to have intrinsically better survival? Although these questions are germane, they are presently unanswerable. It is possible that rate response was programmed on to a group fated to do better anyway, but it is not clear a priori how one could determine that. Future controlled studies may be able to answer this.

Conclusions

The HRSc predicts mortality in a large cohort of CRT-D patients. Reducing the HRSc, through adoption of DDDR, is associated with markedly decreased mortality in patients with high HRSc and presumed chronotropic incompetence. These are the first data that indicate a survival benefit with rate-response programming when properly targeting a high-risk CRT-D population. Because this report is observational, a prospective, randomized, controlled clinical trial will be needed to confirm these initial observations.

Disclosures

Dr Olshansky has received honoraria and, thus, has the following to disclose: Biotronik, Boehringer-Ingelheim, Amarin, On-X, and Daiichi Sankyo (all <$10,000) and Lundbeck (>$10,000). Dr Richards has received honoraria and, thus, has the following to disclose: (all <$10,000) Medtronic, Boston Scientific, Biotronik, Janssen, Boehringer-Ingelheim, Bristol Myers Squibb, and Pfizer. Dr Sharma has received salary and stock from Boston Scientific (> $10,000). W. N. Wold has received salary and stock from Boston Scientific (> $10,000). P. Jones has received salary and stock from Boston Scientific (> $10,000). Dr Perschbacher has received salary and stock from Boston Scientific (> $10,000). Dr Wilkoff has received honoraria and, thus, has the following to disclose: St Jude Medical, Boston Scientific, and Spectranetics (all <$10,000).

References


Survival After Rate-Responsive Programming in Patients With Cardiac Resynchronization Therapy-Defibrillator Implants Is Associated With a Novel Parameter: The Heart Rate Score

Brian Olshansky, Mark Richards, Arjun Sharma, Nicholas Wold, Paul Jones, David Perschbacher and Bruce L. Wilkoff

_Circ Arrhythm Electrophysiol_. 2016;9:
doi: 10.1161/CIRCEP.115.003806

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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