Heart Rate Predicts Outcomes in an Implantable Cardioverter-Defibrillator Population

Mastaneh Ahmadi-Kashani, MD; David J. Kessler, MD; John Day, MD; T. Jared Bunch, MD; Kira Q. Stolen, PhD; Scott Brown, PhD; Salam Sbaity, MD; Brian Olshansky, MD; on behalf of the INTRINSIC RV Study Investigators

Background—Elevated heart rate (HR) is associated with adverse cardiovascular events and total mortality in the general population and in individuals with heart disease. Our hypothesis was that mean HR predicts total mortality and heart failure hospitalization in patients undergoing implantable cardioverter-defibrillator (ICD) implantation.

Methods and Results—The Inhibition of Unnecessary RV Pacing With AV Search Hysteresis in ICDs (INTRINSIC RV) trial included 1530 patients undergoing ICD implantation. After implantation of a dual-chamber ICD, patients were followed for a mean of 10.4 months. The mean HR for 1436 patients over the follow-up period was determined from device histograms. Patients were grouped into strata by mean HR, and the relationship between the primary end point and mean HR was analyzed with Mantel-Haenszel ordinal tests. Higher intrinsic (unpaced) HR was associated with greater risk of achieving the primary end point of death or heart failure hospitalization ($P<0.001$). Of patients with a mean HR $<75$ bpm, 5.8% died or were hospitalized for heart failure, whereas 20.9% with a mean HR $>90$ bpm achieved the same end point, a 3.6-fold difference ($P<0.0001$). In a multivariate model with the use of Cox regression, HR was a significant predictor with a hazard ratio of 1.34 ($P=0.0001$; 95% confidence interval, 1.19 to 1.50), as were age, New York Heart Association functional class, and percent right ventricular pacing, but it was independent of gender and β-blocker dosing. When considered as continuous or discrete variables grouped by 5-bpm increments, HR remained a significant predictor.

Conclusions—In this ICD population, the mean intrinsic HR was strongly associated with outcomes.

Clinical Trial Registration—http://www.clinicaltrials.gov. Identifier: NCT00148967.

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Key Words: defibrillators ■ heart failure ■ heart rate ■ hospitalization ■ survival

Faster heart rate (HR) has been associated with all-cause mortality, sudden death, and other adverse outcomes in the general population and in patients with heart disease.$^{1-3}$ Much of these data are epidemiological and involve isolated HR measurements that do not take into account transient factors such as caffeine or anxiety, which may affect HR and ultimately its predictive value. Additionally, HR measurements at rest, peak exercise, and recovery from exercise may all be prognostic in specific populations.$^{4,5}$ Any change in baseline HR over time may also be prognostic.$^6$ The best HR measurement is unknown, may be population dependent, and may require a comprehensive view determined by a mean value. In addition, the mean HR will eliminate the confounding effects of transient factors. Some implantable cardioverter-defibrillators (ICDs) can measure mean HR over long periods of time, but the importance of HR as a predictor of outcomes in an ICD population is unknown.

Clinical Perspective on p 2045

The Inhibition of Unnecessary RV Pacing With AV Search Hysteresis in ICDs (INTRINSIC RV) trial was a randomized controlled clinical trial of patients who received ICDs for standard clinical indications.$^7$ Using the INTRINSIC RV database, we tested the hypothesis that the mean intrinsic (unpaced) HR, based on data recorded over the entire follow-up, predicted total mortality and heart failure hospitalization.

Methods

The INTRINSIC RV Trial included 108 centers. Inclusion in the study required that patients meet standard accepted criteria for ICD implantation. These criteria included the presence of spontaneous or inducible life-threatening ventricular tachyarrhythmias (secondary prevention) or impaired ventricular function with or without ischemia (primary prevention). All patients received Vitality AVT ICDs capable of recording atrial and ventricular rates throughout the entire follow-up period regardless of pacing programming.$^7$ Patients with...
long-standing atrial fibrillation were excluded. After implantation, all ICDs were programmed to a dual-chamber, rate-responsive mode (DDD) with an atrial pacing rate of 60 to 130 bpm with atrioventricular stress-sensing AVSH (AVSH).

At the 1-week follow-up visit, patients were pacing in the right ventricle <20% of the time were randomized to either DDDR with AVSH 60 to 130 bpm or single-chamber backup ventricular pacing (VVI) 40-bpm programming. If the right ventricle was paced with AVSH 60 to 130 bpm or single-chamber backup ventricular pacing (VVI) 40-bpm programming.8 If the right ventricle was paced to the AVSH >60 bpm, increasing by increments of 5 bpm, up to and including >90 bpm. Analyses included consideration of HR as the mean intrinsic atrial rate and the mean intrinsic ventricular rate. We also compared the event rate on the basis of the mean intrinsic ventricular rate stratified by gender. Relationships between HR and outcomes were evaluated with the use of Mantel-Haenszel ordinal χ2 tests. The Fisher exact test was used for comparisons of discrete variables including proportions of subjects taking β-blockers by gender, clinical history, medications, and gender by inclusion in the present analysis cohort. We used t tests for continuous variables, including HR by β-blocker use and age. ANOVA was used to test the effect of β-blocker dosing on HR and changes in HR over time. β-Blocker dosing levels were categorized into low, medium, and high in a blinded fashion (Table 2). HRs of each patient at each visit were compared with a repeated-measures ANOVA to evaluate the possibility of a time trend. Cox proportional hazards regression was performed to test relationships between HR and outcomes in the presence of baseline covariates such as right ventricular pacing, gender, age, and clinical and arrhythmia history; these were reported as hazard ratios. On the basis of clinical interest and prior suggestive data relating gender, β-blocker dosage, and HR, gender and β-blocker dosage were retained in the model. For purposes of these analyses, HR was included as a continuous predictor of outcomes. Statistical analyses were performed with the use of SAS versions 9.1 and 9.2 (SAS Institute, Cary, NC). All P values are 2-sided; values <0.05 were regarded as statistically significant.

### Results

Mean intrinsic HR, based on ventricular-sensed events, was strongly associated with the primary composite end point (Figure 1). Patients with slower mean intrinsic HR had substantially lower event rates than those with a faster mean intrinsic HR. Over a mean follow-up of 10.4 months, the overall event rate for the 3 slowest HR groups (<75 bpm) was 5.8% versus 20.9% for the fastest HR group (>90 bpm), a 3.6-fold difference in events (P<0.0001). Event rates increased most dramatically in patients whose mean HR was >75 bpm compared with those whose HR was <75 bpm. All analyses of HR involved mean values recorded over the course of the entire follow-up. HR measurements were evaluated by interrogation of the ICDs at each follow-up visit.
At the 3-, 6-, and 12-month visits, there were small differences in mean HR (75.8, 75.6, and 75.0 bpm, respectively) that were not statistically significant. Thus, the mean HR taken over the course of the study is a reasonable predictor of event rates.

Considered in a multivariate model, by Cox regression analysis, HR was a significant predictor with a hazard ratio of 1.34 (P<0.0001; 95% confidence interval, 1.19 to 1.50). Right ventricular pacing, age, and New York Heart Association (NYHA) functional class were also predictors of outcomes independent of other baseline characteristics including blood pressure, gender, β-blocker use and dosing level, arrhythmia, and heart disease history. In this analysis, higher HR, greater degrees of right ventricular pacing, lower NYHA functional class, and advancing age were associated with a greater occurrence of the primary composite end point (Table 3). In this model, HR was considered a continuous predictor; the same model incorporating HR as a discrete variable (grouped by increments of 5 bpm as described above) produced similar results, with HR again a highly significant predictor of events (P<0.0001). Because patients were enrolled at multiple clinical centers, a model incorporating the potential clustering effect by site with the use of generalized estimating equations was also employed for sensitivity purposes. Statistical inference was unchanged under this model.

Prior data suggest that HR in women has a different predictive value than in men. We found the association of higher HR with the primary composite end point to be independent of gender. Even though women had higher event rates, HR predicted outcomes similarly in men and women (P=0.11; Figure 2). Although the potential for an interaction effect is apparent in Figure 2, a statistical evaluation of that interaction showed it to be nonsignificant.

Intrinsic ventricular HR may provide results that differ from atrial rates. For this reason, intrinsic atrial rates and atrial paced rates were also evaluated. Figure 3 shows the relationship between intrinsic atrial HR and the primary composite end point. These results mirror those of intrinsic ventricular rates. Conversely, atrial paced rates were not associated with the primary composite end point (P=0.27).

With the possibility that intrinsic HR may simply reflect sympathetic tone, we considered the impact of β-blockers on outcomes independent of HR. β-Blockers were not prescribed to 337 (23%) of the patients at the time of ICD implantation. The mean HR of those prescribed β-blockers was 75.1±10.6 bpm in contrast to 77.7±12.2 bpm for the remaining patients (P<0.01). These data suggest that HR differences may reflect sympathetic tone, at least in part, and thus may affect outcomes. When dosing is considered, β-blocker use across different β-blockers was collapsed into none, low, medium, and high, as shown in Table 2. Dosing levels for β-blockers in a univariate model were investigated, resulting in a relationship between dosage and event rates with those patients prescribed no β-blockade having significantly more events compared with patients prescribed a high dose of β-blockade (P=0.002). On further exploration of the impact of β-blocker dose on HR, the results were similar, that is, as dosage increased, HR decreased (P<0.001). However, when β-blockers were added to the Cox regression model and in the

Table 3. Predictors of Death and Heart Failure Hospitalization Using Cox Regression Modeling

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, per 10 bpm</td>
<td>0.0001</td>
<td>1.34</td>
<td>1.19–1.50</td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>0.040</td>
<td>1.19</td>
<td>1.01–1.40</td>
</tr>
<tr>
<td>Right ventricular pacing (per 10%)</td>
<td>0.013</td>
<td>1.07</td>
<td>1.02–1.14</td>
</tr>
<tr>
<td>Gender, male</td>
<td>0.083</td>
<td>0.69</td>
<td>0.46–1.05</td>
</tr>
<tr>
<td>NYHA classification</td>
<td>0.0006</td>
<td>1.55</td>
<td>1.21–1.99</td>
</tr>
<tr>
<td>β-Blocker dosing level</td>
<td>0.17</td>
<td>0.87</td>
<td>0.71–1.06</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

Figure 1. Event rate by intrinsic ventricular rate.

Figure 2. Event rate by intrinsic ventricular rate and gender.

Figure 3. Event rate by intrinsic atrial rate.
Table 4. Association Between NYHA Functional Class and HR

<table>
<thead>
<tr>
<th>HR, bpm</th>
<th>NYHA I (n = 297)</th>
<th>NYHA II (n = 790)</th>
<th>NYHA III/IV (n = 309)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>5/51 (9.8)</td>
<td>9/121 (7.44)</td>
<td>2/48 (4.17)</td>
</tr>
<tr>
<td>65–70</td>
<td>1/62 (1.61)</td>
<td>7/129 (5.43)</td>
<td>5/43 (11.63)</td>
</tr>
<tr>
<td>70–75</td>
<td>1/58 (1.72)</td>
<td>8/164 (4.88)</td>
<td>6/61 (9.84)</td>
</tr>
<tr>
<td>75–80</td>
<td>2/56 (3.57)</td>
<td>11/123 (8.94)</td>
<td>5/41 (12.20)</td>
</tr>
<tr>
<td>80–85</td>
<td>2/31 (6.45)</td>
<td>9/118 (7.63)</td>
<td>10/31 (32.26)</td>
</tr>
<tr>
<td>85–90</td>
<td>3/22 (13.64)</td>
<td>7/60 (11.67)</td>
<td>7/37 (18.92)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>4/17 (23.53)</td>
<td>12/75 (16.00)</td>
<td>13/48 (27.08)</td>
</tr>
<tr>
<td>P</td>
<td>0.0397</td>
<td>0.0109</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Values are n (%) except for P values.

Discussion

This is the first report to associate HR with clinical outcomes in an ICD population. The mean intrinsic HR was associated with the primary composite end point of heart failure hospitalization and total mortality. Faster HR was an independent predictor of adverse outcomes. In our study, the intrinsic HR was defined as the mean ventricular (unpaced) rate. We also considered the mean unpaced atrial rate and found the outcomes to be similar. Atrial pacing had no impact on outcomes. These data raise several important issues.

Epidemiological long-term follow-up studies of several populations have shown HR to be associated with outcomes including increased mortality, sudden death, and atrial fibrillation.

The relationship between HR and outcomes is present in general populations, in men, in patients with heart disease, in patients with hypertension, in patients with coronary artery disease, and in patients with heart failure. Not all previous studies have controlled for other important concomitant variables before the measurement of HR. Furthermore, although carefully controlled randomized trials of HR have been performed in other populations, no data have specifically considered a population of ICD recipients. An additional unique quality of our study was the assessment of mean HR over the entire follow-up period. We also analyzed outcomes on the basis of percentage of atrial or ventricular pacing. Compared with several clinical predictors such as age, right ventricular pacing, β-blocker use, gender, and NYHA functional class, intrinsic HR was found to be a powerful predictor of adverse outcomes.

The cause for the relationship between HR and outcomes is uncertain. Although persistent rapid HR in the tachycardia range is potentially harmful, the INTRINSIC RV analysis has shown that HR even in the normal range may be associated with adverse effects. Faster HR may have direct damaging effects on vascular function, myocyte remodeling, coronary atherosclerosis, muscle mass, and plaque disruption. Faster HR can induce ischemia, and, conversely, slowing the HR can have protective effects.

Alternatively, HR may simply be a marker of autonomic function. Sympathetic activation increases HR but may increase mortality by mechanisms other than HR. Sympathetic activation and direct catecholamine stimulation increase myocardial oxygen demand and contractility and therefore can have direct damaging effects on the myocardium. Additionally, catecholamine excess may have direct toxic effects on the heart and vasculature. This can be offset by β-blocker use.

In the INTRINSIC RV Trial, β-blocker use did not negate the predictive effect of HR on outcomes; in contrast, β-blocker use appears to reduce death and heart failure hospitalization by lowering HR. However, β-blocker use likely did not eliminate all effects on sympathetic stimulation. Patients who were not prescribed β-blockers at all may have been a sicker group that could not tolerate this class of medication. Sicker patients may have had higher HR independent of maximal β-blocker dosing. Increased sympathetic tone may be an indicator of the degree of myocardial compensation and may be associated with evidence for worsening heart failure.

Conversely, parasympathetic activation associated with HR slowing can be protective by several potential mechanisms. Decreased parasympathetic tone, as it may occur in patients with chronic heart failure, may be associated with a greater degree of impairment in ventricular function and result in sudden death.

It is likely that there is a dynamic interaction between the loss of parasympathetic tone and excess sympathetic activation, which increases mean intrinsic HR and decreases survival. It is difficult to determine which factors, specifically in regard to autonomic tone, could be responsible for outcomes in these patients. We could not differentiate a specific relationship between parasympathetic and sympathetic tone in the INTRINSIC RV Trial.

The relationship between NYHA functional class and HR was complex. Faster HR may be an indicator of worsening heart failure because patients with a poorer functional class had faster HR and higher event rates. Independent of functional class, however, HR predicted outcomes. This may reflect perturbations in the parasympathetic tone and sympathetic activation as described above. Another possibility may be that increased HR can be a direct contributor to ischemia.
that subsequently increases the risk of hospitalization and increases the risks of cardiovascular and total mortality.

In addition to analyzing the relationships between HR, autonomic tone, and heart failure, we evaluated differences between outcomes based on gender. Although the predictive value of HR has been reported to be less in women than in men on the basis of epidemiological data, in the INTRINSIC RV Trial, we found men and women to have similar outcomes for any given HR. Furthermore, at the extremes of HR elevation, the mortality in women exceeded that of men. Perhaps our study was underpowered to detect a significant difference between men and women in regard to HR and outcomes, largely because of the lower number of women enrolled. On the other hand, perhaps there are no gender-specific differences relative to HR and outcomes, as suggested by our study. This could have been due to specific clinical characteristics of the female population, including older age, more comorbidities, less β-blocker use (71% versus 77%; \( P = 0.039 \)), and lower doses of β-blockers.

By assessing atrial paced rate alone, independent of specific clinical features, we further considered the direct effects of HR on outcomes. The lack of apparent relationship between atrial pacing and outcomes suggests that the intrinsic rate alone is the predictive parameter. These data are consistent with those of the Dual Chamber and VVI Implantable Defibrillator Trial II (DAVID II), which showed that atrial pacing did not affect outcomes despite increasing the HR. Our data are also consistent with the morBidity-mortality EviAlUaTion of the \( l \) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial, which showed that slowing the atrial rate, independent of alterations in autonomic tone, does not affect outcomes. On the basis of the results of our study, rate-responsive atrial pacing appears to be safe.

The interrelationships between HR, autonomic tone, clinical variables, and outcomes are complex and not completely understood. HR remains a key vital sign; it is measured routinely but is often overlooked and has important prognostic value, which may be of great consequence in patients with ICDs. Further exploration of the effects of HR and of the mechanisms by which HR affects morbidity (including atrial fibrillation) and mortality is vital. Perhaps intermittent snapshots of HR assessed at clinical visits or by monitoring via the Internet can provide additional clues into changes in a patient’s condition. It remains to be seen whether access to HR trends facilitates clinical decision making.

We now know that “pretachycardia” (HR 75 to 100 bpm) may be detrimental in ICD patients. Similar to the evolving concepts of borderline diabetes mellitus and prehypertension, perhaps it is time to redefine tachycardia. Using the available technology that cardiac devices offer, we can now critically evaluate pretachycardia.

Limitations

This was a retrospective analysis of data from an international, prospective, multicenter, controlled clinical trial, but it may not necessarily reflect the outcomes in all patients who require an ICD. In addition, the accuracy of the mean HR data was based on atrial and ventricular rates recorded by and interrogated from the ICDs. Longer follow-up may provide results that differ. Mechanisms of the effects seen are uncertain.

Additionally, left ventricular ejection fraction data collection was not mandated in this trial. The primary purpose of the INTRINSIC RV trial was to evaluate single- versus dual-chamber programming in a population that had already met standard indications for ICD implantation. Because patients with chronic atrial fibrillation could not benefit from dual-chamber programming, they were excluded from the INTRINSIC RV trial, and we therefore cannot extend these findings to this population. Furthermore, the follow-up period was relatively short; however, even in this time frame, a significant relationship between HR and events was shown. The success of rapid enrollment, making this one of the largest ICD trials to date, was in part related to the simplicity of its design, which focused on ICD programming characteristics. In retrospect, it is regrettable that we cannot correlate left ventricular ejection fraction with HR.

Conclusion

In an ICD population, intrinsic (unpaced) HR is strongly associated with the composite end point of heart failure hospitalization and total mortality. Intrinsic HR predicts outcomes independent of other clinical characteristics. HR remains an underutilized, but easily determined, and important clinical predictor in this population.

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Disclosures

Dr Day reports honoraria from Boston Scientific CRM and St. Jude; Dr Bunch, honoraria from Boston Scientific CRM; Dr Stolen, ownership interest in and an employee of Boston Scientific CRM; Dr Brown, an employee of The Integra Group, a consultant company for Boston Scientific CRM; and Dr Olshansky, honoraria and/or consultant with Boston Scientific CRM, Medtronic, St. Jude, and BioControl. The remaining authors report no conflicts.

References

Heart Rate Predicts Outcomes

Ahmadi-Kashani et al

Faster heart rate (HR) has been associated with all-cause mortality, sudden death, and other adverse outcomes in the general population and in patients with heart disease. The relationship between intrinsic (unpaced) HR, continuously measured by an implanted device, and clinical outcomes was assessed in a large implantable cardioverter-defibrillator population. In these subjects, higher HR was associated with greater risk of death or heart failure hospitalization, with those patients exhibiting a mean HR >90 bpm experiencing almost a 4-fold difference in events compared with those patients with mean HR <75 ppm. For patients with implantable cardioverter-defibrillators, HR data can predict outcomes in patients with implantable cardioverter-defibrillators. β-Blockers appear to reduce events in a direct relationship to HR. Access to HR trends in patients with implantable cardioverter-defibrillators may assist clinical decision making. HR remains an underutilized, but easily determined, and important clinical predictor in this population.
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