Continuous Autonomic Assessment in Patients With Symptomatic Heart Failure
Prognostic Value of Heart Rate Variability Measured by an Implanted Cardiac Resynchronization Device

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Background—Heart rate variability (HRV) as an indirect autonomic assessment provides prognostic information when measured over short time periods in patients with heart failure. Long-term continuous HRV can be measured from an implantable device, but the clinical value of these measurements is unknown.

Methods and Results—A total of 397 patients with New York Heart Association class III or IV heart failure were studied. Of these, 370 patients had information from their implanted cardiac resynchronization device for mortality risk stratification, and 288 patients had information for measured parameters (ie, HRV, night heart rate, and patient activity) and clinical event analyses. Continuous HRV was measured as the standard deviation of 5-minute median atrial-atrial intervals (SDAAM) sensed by the device. SDAAM <50 ms when averaged over 4 weeks was associated with increased mortality risk (hazard ratio 3.20, \( P = 0.02 \)) and SDAAM were persistently lower over the entire follow-up period in patients who required hospitalization or died. SDAAM decreased a median of 16 days before hospitalization and returned to baseline after treatment. Automated detection of decreases in SDAAM was 70% sensitive in detecting cardiovascular hospitalization, with 2.4 false-positives per patient-year of follow-up.

Conclusions—This study demonstrates that SDAAM continuously measured from an implanted cardiac resynchronization device is lower in patients at high mortality and hospitalization risk. SDAAM declines as patient status decompensates. Continuous long-term SDAAM may be a useful tool in the clinical management of patients with chronic heart failure.

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Key Words: heart failure ■ heart rate ■ mortality ■ trials ■ nervous system, autonomic

Close clinical monitoring of patients with chronic heart failure significantly reduces hospitalization risk and improves quality of life.1–3 Traditionally, close clinical monitoring is achieved by frequent physical assessments in an organized disease-management program.1–3 Recent technological advancements raise the possibility that remotely acquired physiological data from permanently implanted devices may contribute to heart failure patient management.4,5 This approach may provide meaningful information about patient status with a possible decrease in healthcare utilization.5

Heart rate variability (HRV) is a physiological marker of cardiac autonomic control that provides prognostic information about mortality risk.6–10 Recently, HRV was measured with an implanted device, demonstrating that long-term HRV measurement was possible and that cardiac resynchronization therapy resulted in a shift of autonomic control away from sympathetic dominance.4 However, the prognostic value of long-term HRV measurements derived from an implanted device remains unclear, especially when one considers the role of HRV in regard to patient management. The present study examined a long-term measure of HRV, the standard deviation of a 5-minute median atrial-atrial sensed interval (SDAAM), with correlation to mortality and hospitalization risk.

Methods

Patient Population
All US InSync III clinical study patients who received a cardiac resynchronization device (InSync III, model 8042, Medtronic, Inc) for standard indications were screened for this study. Patients included in the InSync III study were in New York Heart Association
(NYHA) functional class III or IV and had received stable, optimal medical therapy for at least 1 month before enrollment, with QRS duration ≥130 ms, left ventricular ejection fraction ≤35%, and left ventricular end-diastolic dimension ≥55 mm. Inclusion and exclusion criteria for the present study were identical to those of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial.1 Patients provided informed consent to be involved in this trial, and each site’s Institutional Review Board reviewed and approved the study. Study enrollment began on November 30, 2000, and the final patient was enrolled June 4, 2002. There were 397 successful implantations of the InSync III system. Patients with save-to-disk data available for specified time periods were included in the study. Save-to-disk data were available if at least 4 daily values were available for applicable weeks.

HRV, Night Heart Rate, and Patient Activity Parameters

HRV was measured prospectively from the atrial sensed cycle length acquired continuously from the implanted cardiac resynchronization device. All patients in the present study received cardiac resynchronization therapy continuously throughout the follow-up period. Individuals responsible for heart rate parameter measurements were not aware of patients’ clinical status. In brief, atrial sensed cycle lengths were measured, and 5-minute A-A interval median values were computed. HRV was then defined as the SDAAM values for each entire 24-hour period. The daily SDAAM was stored and included as a component of a rolling trend analysis, which continuously accumulated data for 6 months. If the patient experienced atrial high-rate episodes (including atrial fibrillation) or had atrial pacing for more than 80% of the 24-hour period, SDAAM from that day was excluded from the analysis. The first 4 weeks after implantation were excluded to allow patients to return to normal lifestyle after the surgery. Data from the SDAAM analysis were uplinked by a programmer at a clinic visit.

The potential clinical value of the SDAAM was evaluated in 3 ways. First, the average SDAAM from weeks 5 to 8 after implantation was used to test the hypothesis that longer-term, device-based SDAAM values are associated with risk for mortality or hospitalizations. For mortality risk stratification, patients were stratified on the basis of their 4-week SDAAM values into 3 groups: (1) low SDAAM (<50 ms), (2) intermediate SDAAM (between 50 and 100 ms), and (3) high SDAAM (>100 ms). These values were chosen on the basis of previous studies6,7 with short-term HRV to determine whether long-term HRV performed in a similar fashion as short-term HRV. Deaths were recorded, and Kaplan-Meier survival curves were constructed.

Second, to determine whether SDAAM was different between groups at high and low risk for subsequent clinical decompensation, SDAAM was compared among patients who were classified into 3 groups on the basis of their 18-month outcomes: (1) no clinical decompensation, (2) minor exacerbations not requiring hospitalization, and (3) cardiovascular hospitalization or death. Events were recorded prospectively. An event was classified as a minor exacerbation if the patient experienced shortness of breath, dyspnea, peripheral edema, dehydration, inadequate cardiac output, or syncope and was treated with an adjustment of diuretic doses or other clinical measures commonly used to treat heart failure acute decompensation.

The third evaluation tested the hypothesis that continuously acquired SDAAM changes as heart failure patients decline clinically. To test this hypothesis, an algorithm was developed to detect decreases in the trend of SDAAM daily values over time. For this analysis, patients were classified into 2 groups: (1) hospitalized for cardiovascular reasons or (2) no clinical decompensation/not hospitalized in the 18-month follow-up period. Patients were excluded from the latter group if they had frequent changes in B-blocker therapy during the 12 months after device implantation. Patients were included in the former group if they had at least 100 days after implantation before hospitalization and if they had save-to-disk data available for the 12 weeks before hospitalization.

For comparison purposes, the association between hospitalization events and changes in the night heart rate and patient activity trends was also determined. Night heart rate was defined as the average ventricular rate between midnight and 4 AM, excluding atrial high-rate episodes. The activity sensor in the implanted device accumulated the number of activity counts sensed in each minute. A minute was considered “active” if the counts exceeded a threshold that corresponded to a walk rate of ~70 steps per minute.

SDAAM, Night Heart Rate, and Activity Change Detection Algorithm

To determine the clinical value of device-based SDAAM, night heart rate, and patient activity, a detection algorithm was developed with a randomly selected subset of the patients with and without hospitalizations in the 18-month follow-up period (development database) and then validated in the remaining patients (validation database). The algorithm was applied retrospectively to SDAAM, night heart rate, and activity data but was designed for daily prospective application as the data were acquired. The algorithm consisted of 3 processing steps that were computed daily, summarized in Figure 1. First, an adaptive reference value was updated daily to track recently measured values and approximate the patient’s expected value (Figure 1, dashed line, upper panel). Second, the accumulated difference between the reference value and the measured value was computed (Figure 1, bottom panel, dotted line). The accumulated difference decreased over time whenever the measured value was less than the reference value. Finally, a threshold for the accumulated difference was established (Figure 1, bottom panel, dashed line), and a change in the parameter was defined when the threshold was exceeded.

The detection algorithm was evaluated by calculating sensitivity (ie, algorithm detection in advance of hospitalization events) and false-negative rates (ie, algorithm detection in the absence of hospitalization events) in the validation database. Detection was considered a true positive when the accumulated difference exceeded the threshold value before hospitalization and remained in excess of the threshold for each day before hospitalization. The exemplary threshold used in this analysis for SDAAM was 200 ms days. This threshold was selected to optimize the predictive value of the algorithm determined as the best trade-off between sensitivity and false-alarm rate. If the accumulated difference did not exceed the threshold on the day of hospitalization it was considered a false-negative detection. False-negative detections were considered as any time the accumulated difference exceeded the threshold in a patient who did not have a hospitalization. If false-positive detections were continuous over days, the initial detection was considered the false-positive event. A new false-positive event was considered only when the accumulated difference returned to baseline and subsequently crossed the threshold again. The resulting number of false-positive detections was divided by the total duration of the data set and was expressed as the number of false-positives per patient.
Clinical Characteristics of the 288 Patients Included in the Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Heart Failure (n=139)</th>
<th>Minor Events (n=71)</th>
<th>Heart Failure Hospitalizations (n=78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66±11</td>
<td>65±12</td>
<td>66±9</td>
<td>0.864</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>61</td>
<td>49</td>
<td>63</td>
<td>0.117</td>
</tr>
<tr>
<td>NYHA class III/IV, %</td>
<td>96/4</td>
<td>92/8</td>
<td>85/15</td>
<td>0.009</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22±6</td>
<td>22±7</td>
<td>21±7</td>
<td>0.369</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>68±9</td>
<td>68±9</td>
<td>70±9</td>
<td>0.413</td>
</tr>
<tr>
<td>Ischemic HF etiology, %</td>
<td>49</td>
<td>38</td>
<td>53</td>
<td>0.177</td>
</tr>
<tr>
<td>QRS width, ms</td>
<td>166±22</td>
<td>165±24</td>
<td>163±21</td>
<td>0.786</td>
</tr>
<tr>
<td>β-Blocker use, %</td>
<td>81</td>
<td>70</td>
<td>55</td>
<td>0.0004</td>
</tr>
<tr>
<td>ACE inhibitor use, %</td>
<td>91</td>
<td>90</td>
<td>88</td>
<td>0.786</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; and HF, heart failure.

SDAAM and Mortality Risk
Of the 397 patients in the trial, 370 had SDAAM values from weeks 5 to 8 after implantation. The 27 patients not included had no save-to-disk information available. Thirty-six patients had SDAAM values <50 ms, 227 were in the intermediate group (SDAAM 50 to 100 ms), and 107 had SDAAM values >100 ms. There were 34 deaths among these patients in the first 12 months after implantation (9% absolute 1-year mortality). All-cause mortality was higher in the low-SDAAM group (SDAAM <50 ms), with a hazard ratio of 3.20 (P=0.02), as shown in Figure 2. The critical events committee adjudicated 25 of these 34 deaths as cardiovascular in origin. For cardiovascular death specifically, the hazard ratio was 4.43 (P=0.01).

Measured Parameters and Clinical Events
In the 288 patients with SDAAM data available, absolute SDAAM values were persistently lower in patients who were hospitalized or who died (74±22 ms) when averaged over weeks 5 to 52 after implantation compared with the other groups (88±25 ms, P=0.0007 for minor event; 90±22 ms, P<0.0001 for no event compared with hospitalization; no statistical difference between minor-event and no-event

Results

Statistical Analysis
Differences in baseline demographics among the groups were analyzed with 1-way ANOVA for continuous variables and the Pearson χ² test for discrete variables. The Cox proportional hazards model was used to estimate the hazard ratio in the survival analysis. The associated probability value corresponds to the null hypothesis that the hazard was the same between groups (ie, hazard ratio=1). Differences in mean values of SDAAM, night heart rate, and patient activity between the groups were compared by ANOVA. Mean differences in SDAAM, night heart rate, and patient activity leading up to hospitalization were evaluated by paired t test. Significance was established at the P=0.05 level. The software used for these analyses was SAS (Statistical Analysis System) version 8.2.

Patient Population for Measured Parameters and Clinical Events Analyses
There were 397 NYHA class III/IV patients with devices implanted in the US InSync III clinical study. Of these, 288 patients had at least 45 of the first 52 weeks of postimplantation save-to-disk data available for the measured parameters and clinical events analyses. Patients who died were included in the analysis if they had at least 4 weeks of save-to-disk data available. Of the 288 patients, 139 patients had no heart failure decompensation, 71 had minor exacerbations that did not require hospitalization, and 78 had cardiovascular hospitalizations or death. Mean follow-up duration for these patients was 16.6±4.0, 16.9±4.3, and 12.6±5.7 months for each group, respectively. There were 38 deaths: 5 in months zero to 3, 8 in months 3 to 6, 8 in months 6 to 9, and 17 thereafter. The remaining 109 patients were not included in the performance analysis because of early cardiovascular death without sufficient save-to-disk data (n=4), noncardiovascular death (n=13), noncompletion of the 12-month follow-up (n=58), or unavailability of save-to-disk information (n=34). Baseline characteristics of the patients included in the present analysis are shown in the Table. Patients in the group with hospitalizations during follow-up were more likely to be NYHA class IV (P=0.009) and less likely to be taking β-blocker therapy at enrollment (P=0.0004).

Figure 2. Kaplan-Meier survival curve for all-cause mortality based on average SDAAM value for weeks 5 to 8 after implantation. There were 36 patients in SDAAM <50 ms group, 227 in 50- to 100-ms group, and 167 in >100-ms group. SDAAM <50 ms when averaged over 4 weeks was associated with increased mortality risk (hazard ratio 3.20, P=0.02).
groups) as shown in Figure 3. SDAAM was not different between hospitalized patients and patients who died (75 ± 25 versus 73 ± 20 ms, P = 0.6). Nighttime heart rate was higher in the patients who were hospitalized or died (73 ± 11 bpm) than in those with minor exacerbations (69 ± 8 bpm, P = 0.05) and individuals without events (69 ± 9 bpm, P = 0.014). Nighttime heart rate was not different between patients who were hospitalized and patients who died (73 ± 10 versus 72 ± 12 bpm, P = 0.5).

Thirty-four patients had cardiovascular hospitalizations at least 100 days after implantation and save-to-disk data for the 12 weeks preceding hospitalization. SDAAM declined before hospitalization from 76 ± 27 ms at baseline (9 to 12 weeks before hospitalization) to 64 ± 26 ms at the time of hospitalization (P < 0.0001). The change in SDAAM before hospitalization was apparent up to 3 weeks before the event, as summarized in the aggregate trends for the 34 patients requiring hospitalization in Figure 4.

Of the 34 patients with hospitalization events, 14 were used to develop the detection algorithm, and 20 were used to validate algorithm performance. The ROC curve for the SDAAM detection algorithm is shown in Figure 5. At a threshold of 200 ms days, a sensitivity rate of 70% was associated with 2.4 false-positive events per patient-year of follow-up. True-positive detections occurred for 70% (7 of 10) of patients undergoing β-blocker therapy and 70% (7 of 10) of patients not receiving β-blocker therapy. The median time between the threshold crossing and hospital admission was 16 days. These results were obtained for a single detection threshold applied to all patients.

Night heart rate increased and patient activity declined as patients approached the time of hospitalization, but the changes were less sensitive than SDAAM (Figure 4). Specifically, night heart rate increased from 75 ± 11 bpm at baseline to 78 ± 11 bpm at the time of hospitalization (P = 0.014). Patient activity declined from 188 ± 109 to 164 ± 118 min/d when baseline values were compared with values at the time of hospitalization (P = 0.028). The ROC curves for night heart rate and patient activity demonstrated lower sensitivity than SDAAM over the entire range of false-positive rates (Figure 5).

**Discussion**

Findings from this study provide insight into autonomic mechanisms of heart failure pathophysiology and develop the hypothesis that autonomic markers, continuously measured by implanted devices, offer meaningful information that may be useful in day-to-day management of heart failure patients. Prior use of HRV was limited by the inability to acquire reliable long-term recordings for more than 48 hours. This substantial limitation can now be overcome by utilizing the long-term information acquired by an implanted device. The use of a cardiac resynchronization device for HRV analysis is a superior method because the device calculates HRV from the atrial sensed activity, ideally without imposing pacing in the atrium, and is able to reliably distinguish non-sinus-initiated aberrancies. Calculation of HRV from atrial sensed depolarization does not require the vagaries of automatic beat discrimination algorithms that significantly alter HRV values. With long-term continuous HRV, then, it is possible to
follow nervous control of the heart when patients are stable and when they decline. This raises the possibility that HRV may actually be a clinical tool that can be used to help manage patients with chronic heart failure.

**Autonomic Mechanisms of Heart Failure**
The pathophysiology underlying heart failure is traditionally thought to be a condition of invariable sympathetic activation and parasympathetic withdrawal arising from decreased cardiac output.\(^\text{13,14}\) Circulating plasma norepinephrine values directly correlate to mortality risk and symptom severity,\(^\text{15}\) but recent basic science data and clinical observations suggest that the reality of autonomic derangements is likely much more complex and individual.\(^\text{16}\) The recent MOXonidine CONgestive heart failure (MOXCON) trial demonstrated harm in patients who had central inhibition of sympathetic outflow even though plasma norepinephrine levels declined dramatically.\(^\text{17}\) In dogs with ischemic left ventricular dysfunction, sympathetic activation only occurred in a group at high risk for sudden death despite similar degrees of left ventricular injury in the low-risk animals.\(^\text{18}\) Therefore, the autonomic response to heart failure represents a complex pathophysiology with mechanisms that have proved difficult to study over time, especially with regard to other hormonal influences on heart rate control. Longer-term HRV, as measured by SDAAM in the present study, may more accurately reflect very-low-frequency oscillations seen in power spectral analysis of heart rate.\(^\text{19}\) Very-low-frequency heart rate oscillations mostly arise from parasympathetic cardiac control but also reflect influences from the renin-angiotensin system.\(^\text{19}\) The SDAAM decline observed in the present study as patients became clinically decompensated likely reflects a combination of sympathetic activation, parasympathetic withdrawal, and renin-angiotensin activation. Which component predominated cannot be determined from this study.

Sympathetic activation was important, however, because patients with more severe symptoms, who were less likely to tolerate β-blocker therapy, had low long-term SDAAM persistently over the 12-month follow-up period. Night heart rate also increased as patients neared decompensation, which supports the possibility of both sympathetic activation and parasympathetic withdrawal, in agreement with other studies.\(^\text{20}\) A decline in patient activity was also observed in the present trial as patient status deteriorated, which may have played a role in the changes observed in the SDAAM parameter.

SDAAM declined several days before hospitalization, which suggests that the neurohormonal control system of the heart detects a change in status and responds long before the patient develops symptoms that would traditionally bring them to the attention of the physician. If this type of insight into the heart’s control system can be monitored continuously, especially with a reliable automatic detection system similar to the one used in the present study, patient monitoring and follow-up could be simplified by obtaining the information from the patient’s home through an Internet link. This type of information processing system is currently available.

**Clinical Utility of Continuous SDAAM Measurement**
Early warning of potential clinical decompensation can be obtained from continuous measurement of right ventricular pressures with a permanently implanted hemodynamic monitoring system.\(^\text{5}\) Implantable hemodynamic monitoring systems are still experimental and are in the midst of clinical validation, but the preliminary data suggest that pressure changes can be detected 4 to 5 days before hospitalization.\(^\text{5}\) Continuous SDAAM measurements may have similar utility and may serve as an accurate early warning system. The clinical response to a decline in SDAAM may simply be to increase the frequency of patient assessment to ensure appropriate volume management. If this is possible, then a reliable means to stratify patient risk may identify which individuals need frequent follow-up. This utility would be very helpful in heart failure treatment programs that serve large patient populations. Automatic surveillance of downloaded information from the patient’s home could flag changes that portend a poor immediate prognosis and notify the physician only when a problem arises. The use of continuous SDAAM would complement traditional use of physical examination, with the possibility of stratifying follow-up needs and clinical assessments when dealing with large numbers of heart failure patients.

**Conclusions**
This study demonstrated that patients with heart failure have stable autonomic activity until they start to decline clinically. Neurohormonal activation, as suggested by a decrease in SDAAM, occurs several days to weeks before patients decompensate enough to require hospitalization. Changes in SDAAM can be tracked with information derived from permanently implanted cardiac resynchronization devices and may provide another means to remotely acquire important physiological information about heart failure patients, which may be helpful in day-to-day management of the syndrome.

**References**


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