Complex Heart Rate Variability and Serum Norepinephrine Levels in Patients With Advanced Heart Failure

MARY A. WOO, DNSc, RN,*† WILLIAM G. STEVENSON, MD, FACC,†
DEBRA K. MOSER, DNSc, RN,* HOLLY R. MIDDLEKAUFF, MD†
Los Angeles, California

Objectives. This study was designed to examine the relation of the Poincaré plot heart rate variability pattern to sympathetic nervous system activity as assessed by serum norepinephrine.

Background. Poincaré plots demonstrate a complexity of beat to beat behavior not readily detected by other heart rate variability measures. Previous studies have described two abnormal Poincaré patterns in patients with heart failure: a torpedo pattern with reduced beat to beat variability and a complex pattern with clustering of points.

Methods. To assess the relation of these plots to sympathetic activity, plasma norepinephrine at rest and a standard deviation measure of heart rate variability were analyzed in 21 patients with heart failure (mean left ventricular ejection fraction ± SD) 0.22 ± 0.08).

Results. Eleven subjects had a torpedo-shaped and 10 subjects had a complex Poincaré plot pattern. These two groups did not differ significantly in age, functional class, disease etiology, left ventricular ejection fraction, heart rate, ventricular ectopic activity or in a standard deviation measure of heart rate variability. However, patients with a complex Poincaré plot pattern had higher norepinephrine levels (722 ± 373 pg/ml) than patients with torpedo-shaped plots (309 ± 134 pg/ml) (p = 0.003). Patients with a complex pattern also had more severe hemodynamic decompensation, as evidenced by their higher levels of pulmonary capillary wedge and mean pulmonary artery pressures and lower values for cardiac index than those of patients with a torpedo-shaped plot.

Conclusions. Complex Poincaré plots are associated with marked sympathetic activation and may provide additional prognostic information and insight into autonomic alterations and sudden cardiac death in patients with heart failure.

(J Am Coll Cardiol 1994;23:565-9)

Poincaré plots have been used to detect nonrandom behavior in a variety of complex systems. Recently, they have been used to assess heart rate variability in sudden infant death syndrome (1), congenital central hypoventilation syndrome (2) and heart failure (3). Poincaré plots are constructed by graphing each sinus RR interval against the next RR interval. The resulting graph provides a qualitative picture of both overlaid and beat to beat RR interval behavior.

In previous studies (3), we examined Poincaré plots in both healthy control subjects and patients with heart failure (3). All healthy control subjects had a similar Poincaré plot pattern (Fig. 1), characterized by increased symmetric RR interval dispersion at the longer RR intervals (slower heart rates). In contrast, patients with heart failure had one of two distinctive Poincaré plot patterns (Fig. 2). The first was a "torpedo-shaped" pattern (Fig. 2, A and B), distinguished by a decreased range of RR interval values and absence of the increased, symmetric RR interval dispersion at longer RR intervals seen in healthy control subjects. The second pattern was "complex" (Fig. 2, C and D), consisting of a thin core area of RR intervals, similar to that seen in the torpedo-shaped patterns, and clusters of RR intervals. We hypothesized that these two types of Poincaré plot patterns indicate different severity of sympathetic activation or autonomic dysfunction in heart failure. Thus, the purpose of this study was to determine the relation of Poincaré plot measures of heart rate variability to serum norepinephrine levels in patients with advanced heart failure.

Methods

Our sample consisted of 21 subjects admitted to University of California at Los Angeles (UCLA) Medical Center for treatment of advanced heart failure. Their demographic data are presented in Table 1. All subjects had a thermodilution pulmonary artery catheter inserted as part of the UCLA standard heart failure treatment and evaluation (4) and were on a regimen of bed rest with bedside commode privileges. All participants were in sinus rhythm and none required
Examples of Poincaré plot patterns from two healthy subjects: a 52-year old man (left) and a 48-year old man (right). The standard deviation measure of heart rate variability values was 126 and 133 ms, respectively. The X axis (RRn) indicates the value of each RR interval, and the Y axis (RRn + 1) is the value of the subsequent RR interval.

Mechanical circulatory or ventilatory support. Exclusion criteria were use of a pacemaker, history of cerebrovascular accident, renal failure, diabetes mellitus, recent (within the last 6 months) myocardial infarction, recent (within the last 2 months) change in antiarrhythmic medication and use of calcium channel blockers or beta-adrenergic blocking agents.

The procedure for all subjects was as follows. Patients were fasting and had not smoked for at least 8 h before the study. Two hours after insertion of a thermodilution pulmonary artery catheter for hemodynamic assessment (usually in the late afternoon), each subject was placed supine in their hospital bed, with the head of the bed at a 30° angle. The patient was left without disturbance by health care staff, family, friends or television for 30 min. At the end of the 30 min, 7 ml of blood was drawn painlessly through the proximal port of the pulmonary artery catheter and inserted immediately into a vial with ethylenediaminetetraacetic acid (EDTA) and stored in ice. The blood sample was then centrifuged at a temperature of 5°C and the serum was immediately frozen at -80°C. The serum samples were later analyzed by the UCLA clinical laboratories using liquid chromatography with electrochemical detection (5). Norepinephrine was drawn at the beginning of the study because the patient’s medical regimen and activity were undisturbed at this point.

A 24-h Holter electrocardiogram (ECG) was initiated immediately after catecholamine samples were obtained. The ECG recordings were scanned in semiautomatic mode (operator confirmation of all beat types) on a Del Mar 750 scanner. The time of beat, beat type and serial RR interval values were then stored on floppy disks for later heart rate variability analysis.

Heart rate variability was assessed by a standard deviation measure (the standard deviation of the square root of the mean of the squared deviations of each RR interval over a 24-h recording period), as described by Kleiger et al. (6), and from Poincaré plots (3). Poincaré plots were constructed using UCLA custom-designed software (3). Poincaré plot construction consisted of plotting each sinus RR interval against its subsequent sinus RR interval. Poincaré plots were categorized by three persons.
who had no knowledge of each subject's demographic and clinical data (100% agreement). The investigator who monitored Poincaré plot construction was not involved in Poincaré plot categorization. Only sinus RR intervals were used for heart rate variability analysis and all RR intervals associated with ectopic activity and artifact were deleted from the analysis.

The data were examined with use of the Student t test (two-tailed) and chi-square analysis. Significance was prospectively set at p < 0.05. Mean values ± SD are presented.

**Results**

Eleven subjects had a torpedo-shaped and 10 had a complex Poincaré plot pattern. These two groups did not differ significantly in age, New York Heart Association functional classification, mean heart rate, disease etiology, left ventricular ejection fraction, right atrial pressure, mean blood pressure, ventricular ectopic activity or serum sodium levels (Table 2). However, the patients with a complex Poincaré plot pattern had more severe hemodynamic decompensation as indicated by their significantly higher values for pulmonary capillary wedge pressure and mean pulmonary artery pressures and lower values for cardiac index than those of patients with a torpedo-shaped plot.

Patients with heart failure with a torpedo-shaped Poincaré plot had significantly lower norepinephrine levels (309 ± 134 pg/ml) than did patients with a complex Poincaré plot (mean 722 ± 373 pg/ml) (p = 0.003) (Fig. 3). There were no significant differences in the standard deviation measure of heart rate variability between the two Poincaré plot configuration groups (81 ± 27 vs. 86 ± 46 ms) (p = 0.75) (Fig. 4).

**Discussion**

Patients with heart failure have autonomic nervous system abnormalities, typified by increased sympathetic activity (7), decreased vagal tone (8–10) and depressed baroreceptor responsiveness (11,12). High sympathetic tone as indicated by elevated norepinephrine levels at rest (13) is

**Table 2. Clinical Characteristics of Subjects With Different Poincaré Plot Patterns**

<table>
<thead>
<tr>
<th></th>
<th>Torpedo Pattern (n = 11)</th>
<th>Complex Pattern (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55 ± 8</td>
<td>54 ± 8</td>
<td>0.91</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1 ± 0.6</td>
<td>3.1 ± 0.6</td>
<td>0.89</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Non-CAD</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>16 ± 7</td>
<td>27 ± 5</td>
<td>0.006*</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.23 ± 0.06</td>
<td>0.22 ± 0.04</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean heart rate (beats/min)</td>
<td>81 ± 13</td>
<td>89 ± 13</td>
<td>0.17</td>
</tr>
<tr>
<td>PVCs/24 h (no.)</td>
<td>1,051 ± 1,333</td>
<td>3,588 ± 5,557</td>
<td>0.16</td>
</tr>
<tr>
<td>RA (mm Hg)</td>
<td>7 ± 4</td>
<td>12 ± 8</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.28 ± 0.31</td>
<td>1.91 ± 0.44</td>
<td>0.04*</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>87 ± 14</td>
<td>83 ± 8</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean PA (mm Hg)</td>
<td>24 ± 9</td>
<td>59 ± 9</td>
<td>0.002*</td>
</tr>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>137 ± 4</td>
<td>135 ± 2</td>
<td>0.30</td>
</tr>
<tr>
<td>ACE inhibitor (yes)</td>
<td>9</td>
<td>7</td>
<td>0.43</td>
</tr>
<tr>
<td>Digoxin (yes)</td>
<td>8</td>
<td>8</td>
<td>0.55</td>
</tr>
<tr>
<td>Antiarrhythmic agents (yes)</td>
<td>2</td>
<td>0</td>
<td>0.26</td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5</td>
<td>5</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Statistically significant at p < 0.05. Values presented are mean value ± SD or number of patients. ACE = angiotensin-converting enzyme; BP = blood pressure; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; NYHA class = New York Heart Association functional class; PA = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVCs/24 h = premature ventricular complexes on the 24-h ambulatory electrocardiogram; RA = right atrial pressure.
predictive of poor survival in patients with heart failure (11,14–16). The low standard deviation measure of heart rate variability in this study is consistent with high sympathetic and low parasympathetic tone in our sample of patients with advanced heart failure.

Nonlinear analysis of heart rate variability. Heart rate variability is determined by a complex interaction of sympathetic and parasympathetic influences, which are modulated by central and peripheral nervous system influences on sinus node automaticity. This may behave as a nonlinear system and give rise to complex phenomena that superficially appear to be random and may elude detection by linear analytic techniques (17–22). The nonlinear technique of Poincaré plot analysis can indicate levels of organization not readily apparent from standard deviation or spectral methods of heart rate variability analysis.

In a previous study (3) we defined normal and two qualitatively different abnormal (torpedo and complex) Poincaré plot patterns in healthy subjects and patients with advanced heart failure. As in the present study, both abnormal Poincaré plot patterns were associated with decreased standard deviation measure of heart rate variability. However, this standard deviation measure of heart rate variability did not distinguish between the two groups. This study demonstrates that the complex Poincaré plot patterns are associated with higher norepinephrine levels, consistent with greater sympathetic activation. These patients also had more severe hemodynamic abnormalities, consistent with more severe heart failure.

Complex Poincaré plots. Inspection of the Poincaré plots reveals that the torpedo-shaped pattern is due to reduced RR interval range and beat to beat variability. The beat to beat RR interval is relatively fixed, but over time the RR intervals can move slowly up and down over a limited range. Hence, the standard deviation measure of heart rate variability is reduced. Complex patterns also have a reduced overall range and high heart rate, with RR intervals tending to converge at the lower left corner (smaller RR intervals) of the graph. However, in contrast to the torpedo-shaped plots, the beat to beat variability in complex patterns is increased with the formation of unusual clusters of RR intervals.

The mechanisms generating complex RR interval plots are unclear. The multiple asymmetric clusters of points suggest an intricate nonlinear system of interaction between the sympathetic and parasympathetic systems in these patients with heart failure. The large beat to beat variations can vary greatly and could possibly indicate parasympathetic fluctuations. It is unlikely that the profound RR interval variations seen in complex plots are due to sympathetic activity, as it reacts less quickly than the parasympathetic nervous system (8,23,24). These marked beat to beat RR interval changes are surprising in patients with sympathetic hyperactivity and low parasympathetic tone. However, this may be consistent with the exaggerated effect of vagal stimulation in the presence of high sympathetic tone known as "accentuated antagonism" (25). Accentuated antagonism has been reported in normal human subjects (26), patients undergoing clinically indicated electrophysiologic testing (27) and animal models (28,29), but to our knowledge it has not been described in patients with heart failure.

Limitations. Our sample size was small and may not have detected other clinical associations with the Poincaré plot patterns. There was only one measure of norepinephrine in each subject because repeated measures were not possible in this study. We applied only one method of standard deviation of heart rate variability in this study, and the relation of other standard deviation measures to Poincaré plots is unknown. We did not utilize spectral analysis measures of heart rate variability because of the frequent ventricular ectopic activity in our subjects. Ventricular ectopic activity was probably not responsible for the unusual RR interval behavior in the complex plots because the RR intervals containing ventricular or atrial ectopic activity were excluded from our Poincaré plot and standard deviation measures of heart rate variability analysis. Moreover, in a previous study, we demonstrated that ventricular ectopic activity did not affect subsequent sinus to sinus RR intervals in patients with advanced heart failure (30).

We cannot exclude the possibility that sinus node abnormalities are more frequent in patients with a complex Poincaré plot pattern. Sinus node dysfunction or sinoatrial node exit block could contribute to the unusual RR interval clustering behavior seen in complex plot patterns. However, our patients did not have bradyarrhythmias or other evidence of sinus node dysfunction on their ECG.

Conclusions. Patients with advanced heart failure with similar functional class, ejection fraction and disease etiology can have marked differences in beat to beat heart rate variability that can be detected in Poincaré plots but not necessarily in standard deviation measures of heart rate variability. Complex Poincaré plots are associated with higher norepinephrine levels, suggesting more severe heart failure, than are torpedo-shaped patterns. Further investigation is warranted to determine if Poincaré plots may provide...
additional prognostic information and insight into autonomic alterations and sudden cardiac death in patients with heart failure.

We thank Lynne W. Stevenson, MD, Director of the Ahmanson-UCLA Cardiomyopathy Clinic and Connie Wright, RN of the UCLA Holter Laboratory for their assistance in this study.

References

30. WOO ET AL. UNIVERSITY. CARDIOLOGY. WOO ET AL. HEART RATE VARIABILITY AND NOREPINEPHRINE WOO ET AL. 569