Heart Rate Turbulence and Clinical Prognosis in Hypertrophic Cardiomyopathy and Myocardial Infarction

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Short-term fluctuations in sinus cycle length after a single ventricular premature complex (VPC) have attracted considerable interest and have been termed heart rate turbulence (HRT). The onset and slope of HRT have each been reported to be independent and powerful predictors of clinical prognosis in patients with myocardial infarction (MI), but there are no data available for patients with hypertrophic cardiomyopathy (HCM). Thus the present study analyzed the 2 HRT variables to determine their prognostic value in HCM patients. Holter monitoring data were obtained from 104 HCM patients, 44 MI patients and 56 normal controls, from which singular VPCs followed by ≥20 normal sinus beats were isolated and the HRT onset and slope were automatically calculated. HRT onset and slope were abnormal in MI patients, but not in HCM patients, as compared with normal control subjects (onset: −1.1±2.9, −2.1±3.4, −1.4±5.1%; slope: 10.6±8.6, 18.0±13.9, 16.6±9.7 ms/beat, respectively). During the follow-up period of 27±10 months, 7 HCM patients and 10 MI patients either died from cardiac death or were hospitalized for congestive heart failure. In MI patients, HRT onset was higher and the HRT slope was lower in patients with cardiac events than in patients without (onset: 1.1±2.7 vs −1.7±2.7%, p=0.011; slope: 5.7±4.3 vs 12.0±9.0 ms/beat, p=0.028). In HCM patients, however, the HRT onset and slope were similar between patients with and without cardiac events (onset: −2.0±2.0 vs −2.1±3.5%, p=0.98; slope: 18.1±10.9 vs 18.0±14.0 ms/beat, p=0.68). In conclusion, unlike MI patients, the HRT variables in selected HCM patients were not abnormal and failed to predict the clinical prognosis. (Circ J 2003; 67: 601–604)

Key Words: Heart rate turbulence; Hypertrophic cardiomyopathy; Prognosis; Ventricular premature complex

Heart rate turbulence (HRT) represents short-term fluctuations in sinus cycle length after a single ventricular premature complex (VPC). Normally, HRT comprises sinus rate acceleration during several beats immediately following a VPC and the subsequent deceleration back to the baseline before the 20th beat. It is now believed that HRT is principally triggered by underlying physiological alterations of cardiac autonomic regulation; a VPC preceded by a short coupling interval results in a sudden drop in blood pressure because of insufficient ventricular filling, with subsequent transient loss of vagal efferent activity leading to sinus rate acceleration.

The early acceleration and late deceleration in sinus cycle length following a VPC are termed the HRT onset and slope, respectively, and are each currently being used in the assessment of HRT. Recently, these variables were reported to be powerful independent predictors of the clinical prognosis in patients with myocardial infarction (MI). However, data for patients with hypertrophic cardiomyopathy (HCM) are not available, so the purpose of the present study was to determine these variables in HCM patients and correlate them with the clinical prognosis.

Methods

Study Population

We studied 104 consecutive ambulatory HCM patients, 44 MI patients and 56 normal controls who were treated at or referred to Matsushita Memorial Hospital during the period of April 2000 to March 2002. All subjects had regular sinus rhythm and were clinically stable. The MI patients and controls were matched to the HCM patients with regard to age and gender distribution. The diagnosis of HCM was based on echocardiographic demonstration of left ventricular (LV) hypertrophy with end-diastolic wall thickness ≥15 mm and LV end-diastolic dimensions ≤55 mm, in the absence of any cardiac or systemic disorder that causes LV hypertrophy. The HCM patient group consisted of 83 men and 21 women with a mean age of 56±13 years; of them 8 had apical hypertrophy, 12 had a family history of sudden death, 17 had episodes of syncope, 34 had ventricular tachycardia defined as 3 or more consecutive VPCs with a frequency >120 beats/min. The maximum LV wall thickness was 22±3 mm and LV fractional shortening was 41±8% on echocardiogram. Eight patients had a Doppler-calculated resting left ventricular outflow tract gradient of at least 30 mmHg. The class of heart failure was New York Heart Association (NYHA) I in 65 patients, II in 38 patients and III in 1 patient.

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All MI patients had a documented history of acute MI or electrocardiographic (ECG) evidence of MI (ie, deep Q-wave). The MI patient group consisted of 34 men and 10 women with a mean age of 58±10 years; ventricular tachycardia was observed in 11 patients; the LV ejection fraction (LVEF) by venticulogram was 32±13%; and LV fractional shortening was 22±10% on echocardiogram; NYHA class was I in 10, II in 29 and III in 5 patients.

Fifty-six healthy subjects served as normal controls; there were 43 men and 13 women with a mean age of 58±15 years; none had any cardiovascular symptoms or history of cardiovascular disease; all exhibited normal 12-lead ECG and echocardiographic findings; LV fractional shortening was 38±6% on echocardiogram.

### HRT Analysis

All study subjects underwent 24-h Holter monitoring. After a manual review of the recorded data, we selected singular VPCs preceded and followed by ≥20 normal sinus beats. The 20 subsequent R-R intervals in the beats following a VPC were measured automatically and the HRT onset or slope was defined as abnormal ≥0% or the slope was ≥2.5 ms/beat. Of all VPCs in 50 HCM patients, the reproducibility of HRT onset or HRT slope was tested on 2 random VPCs in 50 HCM patients. The Spearman rank correlation coefficient was used to determine the HRT onset or slope were extremely skewed, comparisons in any of the 4 HRT variables between HCM patients and controls.

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### Follow-up and End-point

All subjects were followed up, beginning with 24-h Holter ambulatory ECG monitoring. Patient information was obtained from available medical records and interviews with the patients and/or their physicians in charge. Follow-up data were available for all patients. The efficacy end-point was the incidence of cardiac events: cardiac death or heart failure. Cardiac death was defined as death from myocardial infarction, heart failure or arrhythmia, or sudden death. Sudden death was defined as instantaneous and unexpected death within 1 h of the onset of symptoms or an unwitnessed death in a subject previously in a stable condition. Episodes of successfully resuscitated life-threatening arrhythmia were classified as cardiac death. Heart failure was defined as requiring hospitalization for initiation of intravenous treatment with inotropic, vasodilator, and/or diuretics; mechanical ventilation or circulatory support.

### Statistical Analysis

Categorical variables were reported as absolute (percentages), and compared by chi-square test or Fisher’s exact test. Continuous variables were expressed as the mean±standard deviation. Age was compared between the 3 groups by one-way analysis of variance followed by Scheffe’s multiple comparison test. Because the distributions of the HRT slope and onset were extremely skewed, these variables between 2 groups or 3 groups were assessed using the Mann-Whitney U test or Kruskal-Wallis test, respectively. The reproducibility of HRT onset or HRT slope was tested on 2 random VPCs in 50 HCM patients. The Spearman rank correlation coefficient was used to compare the trend analysis. Identification of predictors of cardiac events was based on Cox proportional hazards analysis as risk ratio and 95% confidence interval. A p<0.05 was considered statistically significant.

### Results

Age and gender distribution were similar for the 3 groups (Table 1). The LV fractional shortening was lower in MI patients than in HCM patients or controls. HRT onset did not differ among the 3 groups, but the incidence of abnormal onset tended to be higher in MI patients than in HCM patients or controls (35%, 20%, and 19%, respectively; p=0.099). The HRT slope was lower in MI patients than in HCM patients or controls (10.6±8.6, 16.6±9.7, respectively; p=0.00084). Similarly, the incidence of abnormal HRT slope was more frequent in MI patients than in HCM patients or controls (14%, 3%, 0%, respectively; p=0.0026). There were no significant differences in any of the 4 HRT variables between HCM patients and controls.

There was a significant correlation in the HRT onset (r=0.63, p=0.0006), mean differences 0.1±4.3) and HRT slope (r=0.68, p<0.0001), mean differences 2.6±9.8) between measurements made for different VPCs. The concordance rate of abnormal HRT onset or HRT slope was 96% or 88%, respectively.

During the follow-up period of 27±10 months, cardiac events occurred in 7 HCM patients and 10 MI patients, but not in any of the controls. The follow-up period in each group was similar (27±9, 28±11, 26±10 months, respectively). In the HCM group, 1 patient died of progressive heart failure and 6 were hospitalized for congestive heart failure. In the MI group, 1 patient died suddenly from ventricular fibrillation, 5 died of progressive heart failure and 4 were hospitalized for congestive heart failure.

### Table 1 Baseline Characteristics and Heart Rate Turbulence (HRT) Variables in the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>Hypertrophic cardiomyopathy</th>
<th>Myocardial infarction</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>102</td>
<td>43</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56±13</td>
<td>58±10</td>
<td>55±15</td>
<td>0.21</td>
</tr>
<tr>
<td>Male (%)</td>
<td>82 (80)</td>
<td>34 (79)</td>
<td>42 (79)</td>
<td>0.98</td>
</tr>
<tr>
<td>Left ventricular fractional shortening (%)</td>
<td>41±8</td>
<td>22±10*</td>
<td>38±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HRT onset (%)</td>
<td>–2.1±1.4</td>
<td>–1.1±2.9</td>
<td>–1.4±5.1</td>
<td>0.22</td>
</tr>
<tr>
<td>HRT slope (ms/beat)</td>
<td>18.0±13.9</td>
<td>10.6±8.6*</td>
<td>16.6±9.7</td>
<td>0.00084</td>
</tr>
<tr>
<td>Abnormal HRT onset, ≥0% (%)</td>
<td>20 (20)</td>
<td>15 (35)</td>
<td>10 (19)</td>
<td>0.099</td>
</tr>
<tr>
<td>Abnormal HRT slope, ≥2.5 ms/beat (%)</td>
<td>3 (3)</td>
<td>6 (14)*</td>
<td>0 (0)</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

*p<0.01 vs hypertrophic cardiomyopathy or control
Heart Rate Turbulence in HCM

Table 2. Heart Rate Turbulence (HRT) and Outcome in Patients With Hypertrophic Cardiomyopathy or Myocardial Infarction

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
<th>HRT variables according to cardiac events</th>
<th>Association with time to cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (+)</td>
<td>Events (−)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRT onset (%)</td>
<td>1.1±2.7</td>
<td>−1.7±2.7</td>
</tr>
<tr>
<td>HRT slope (ms/beat)</td>
<td>5.7±4.3</td>
<td>12.0±9.0</td>
</tr>
<tr>
<td>Abnormal HRT onset, ≥0% (%)</td>
<td>6 (67)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Abnormal HRT slope, ≤2.5 ms/beat (%)</td>
<td>4 (44)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

CI, confidence interval. *Mann-Whitney U test or chi-square test; †univariate Cox proportional hazards analysis.

Discussion

The major finding of this study was that HRT variables are abnormal and of prognostic value in MI patients, as reported previously.5,6 We may safely consider that the HRT variables were abnormal and of prognostic value, as in HCM patients. In MI patients, on the other hand, the HRT variables remained normal and failed to predict clinical prognosis in selected HCM patients. These findings need to be confirmed in a larger prospective study.

Moreover, Lin et al.11 by systematically inducing VPC in patients without structural heart disease, demonstrated that HRT onset correlated negatively, and HRT slope correlated positively, with baroreflex sensitivity. A recent study of 45 patients with congestive heart failure mainly caused by coronary artery disease or idiopathic dilated cardiomyopathy has shown that the change to HRT correlated well with attenuated baroreflex sensitivity.10 Therefore, attenuated baroreflex sensitivity may evoke the change to HRT via the vagal efferent limb of the baroreflex arc. In conclusion, although HRT variables are abnormal and of prognostic value in MI patients, these variables remained abnormal and failed to predict clinical prognosis in selected HCM patients.
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References


