Effects of Ventricular Premature Stimulus Coupling Interval on Blood Pressure and Heart Rate Turbulence

Mari A. Watanabe, MD, PhD; Joseph E. Marine, MD; Robert Sheldon, MD; Mark E. Josephson, MD

Background—Heart rate turbulence (HRT) is a promising noninvasive risk stratifier for mortality after myocardial infarction. On the basis of a study of ventricular premature complex coupling interval and sympathetic nerve burst amplitude, we hypothesized that measures of HRT would increase with increased prematurity of the coupling interval.

Methods and Results—Twenty-eight patients undergoing programmed electrical stimulation were studied (12 with prior myocardial infarction, aged 60±18 years). An extrastimulus was delivered from the right ventricular apex after 20 sinus beats with a V-S₂ coupling interval decremented by 20 to 30 ms until refractoriness was reached. Turbulence slope (TS), turbulence timing (TT), and turbulence onset were calculated for each extrastimulus, and the linear regressions of these parameters on coupling interval and compensatory pause were calculated. Arterial blood pressure was measured with arterial catheter or a noninvasive continuous blood pressure transducer (Buffington cuff). TS and turbulence onset were abnormal in 4 and 13 patients, respectively. HRT parameters were significantly correlated with coupling interval or compensatory pause in only 2 or 3 patients for a given regression analysis. This absence of correlation was found likely to be due to lack of correlation between compensatory pause and systolic blood pressure after the compensatory pause. Heart rate and TS were correlated: Patients with high heart rate had low TS and late TT (TS = −2.7 + 0.01 × sinus cycle length, P=0.018; TT = 8.8 to 0.005 × sinus cycle length, P=0.013).

Conclusions—HRT can be induced by programmed stimulation. In this setting, heart rate affects HRT but not ventricular premature complex prematurity. Induced HRT seems to be a valid method for measuring HRT parameters in patients with few ventricular premature complexes. (Circulation. 2002;106:325-330.)

Key Words: electrophysiology ■ risk factors ■ death, sudden

The term heart rate turbulence (HRT) was coined to describe the short-term fluctuation in sinus cycle length (SCL) that follows a ventricular premature complex (VPC). In normal subjects, sinus rate accelerates and then decelerates back to baseline after a VPC. Schmidt et al defined 2 parameters, turbulence onset (TO, the amount of sinus acceleration) and turbulence slope (TS, the rate of sinus deceleration), and measured them in Holter recordings taken from a test group of 100 myocardial infarction (MI) survivors to establish normal and abnormal values of these parameters. They then prospectively applied criteria based on these values to Holter recordings taken from 2 large post-MI clinical trials and demonstrated that absence of HRT (abnormal TS and TO) after spontaneous VPCs was more predictive of mortality after MI (relative hazard 3.2) than was other commonly measured noninvasive variables.

The mechanism underlying normal HRT is unknown. On the basis of previous studies, it is likely that the sudden drop in blood pressure with the VPC results in vagal withdrawal and sympathetic recruitment, both of which accelerate sinus rate. The ensuing compensatory pause and increase in blood pressure have the opposite effect (vagal recruitment and sympathetic withdrawal), which leads to sinus deceleration. Because normal HRT consists of sinus acceleration followed by deceleration, a 1- to 2-beat delay between blood pressure change and autonomic effect could explain the pattern of normal HRT. The relative contribution of the 2 limbs of the autonomic nervous system to turbulence measures is also unknown. However, the known shortness of latency and duration of vagal effects and the longer latency and duration of sympathetic effects lead to the conjecture that the short sinus acceleration phase depends more on vagal withdrawal than on sympathetic recruitment and that the latter part of the multibeat duration of sinus deceleration is largely due to sympathetic withdrawal.

The main purpose of the present study was to assess whether HRT, originally defined in 24-hour Holter recordings with the use of spontaneous VPCs, could be observed in the clinical electrophysiology laboratory with the use of paced VPCs (induced HRT). A second purpose of the present study was to systematically assess the relationship between VPC coupling interval, arterial blood pressure, and HRT parame-
ters. On the basis of a study that showed a relationship between VPC prematurity and sympathetic nerve burst amplitude in the peroneal nerve, we hypothesized that measures of HRT would increase with increased prematurity of the VPC coupling interval.

Methods
Twenty-eight patients who were referred to a large urban teaching hospital for electrophysiological study for documented or suspected arrhythmias were studied. All patients gave written informed consent, and the Human Subjects Committee approved the study. VPCs were induced at the right ventricular apex at twice diastolic threshold after every 20 sinus beats during sinus rhythm at various coupling intervals. The first VPC was induced 100 ms prematurely, and subsequent coupling intervals were decremented by 20 to 30 ms until refractoriness was reached. Electrograms were recorded on a standard digital system (Cardiolab, Prucka Engineering, Inc, or Bard Electrophysiology), and VV intervals of the right ventricular apex electrogram were measured by using online calipers at a recording speed of 200 mm/s.

VV intervals were used to calculate TO and TS for each VPC, as defined by Schmidt et al. Briefly, TO was the difference between the mean of the first 2 sinus VV intervals after the compensatory pause and the mean of the 2 sinus VV intervals preceding the VPC, expressed as a percentage of the former. TS was the slope of the steepest regression line between beat number and VV interval. Specifically, a linear regression slope was calculated for the first 5 sinus VV intervals after the compensatory pause (VV1 to VV5), then for VV2 to VVn, then for VV1 to VVn, and so forth. TS was defined as the maximum slope value obtained from this process. We also defined a new third parameter, turbulence timing (TT), as the first beat number of the 5-beat VV sequence giving the maximum regression slope. For example, if the VV2-to-VV6 interval gave the largest slope, TT was given the value 2.

Arterial blood pressure was continuously measured in 10 patients with either arterial catheters (9 patients) or a Buffington cuff (1 patient), which is a noninvasive continuous blood pressure transducer (Buffington Electronics), and displayed with the intracardiac electrograms. The nadir and peak of arterial blood pressure for each beat were measured online.

Clinical data for each patient were abstracted from the medical record, including arrhythmia history, left ventricular ejection fraction (LVEF), history of MI, and New York Heart Association (NYHA) functional class. The relationship between TO, TS, VPC coupling interval, and compensatory pause was analyzed by using a standard statistical software package (StatView 6.0, SAS Institute, Inc). A value of \( P<0.05 \) was considered statistically significant. Data are expressed as mean±SD, except as noted.

Results

Patient Characteristics
The patients were aged 59.9±17.8 years. Seven were women, and 21 were men; 12 had a history of previous MI; the clinical arrhythmia was ventricular tachycardia (VT) in 16 and supraventricular tachycardia (SVT) in 12; and LVEF was ≤40% in 13 and >40% in 10 (LVEF data were unavailable in 5 of the SVT patients, in whom it was presumed to be normal according to clinical data). NYHA class was 2 to 4 in 10 patients. Half of the patients were taking \( \beta \)-blockers, 5 were taking amiodarone, and 5 were taking digoxin. Small doses of midazolam and fentanyl were given to 19 patients during the study to produce anoxiolyis.

The mean number of VPCs evaluated for each patient was 11.9±5.0. For all patients, the average of the mean TS, mean TT, and mean TO values computed for each patient was 10.3±9.0 ms per beat, 4.77±1.81, and −0.8±2.7%, respectively. As defined by the criteria of Schmidt et al., mean TS was abnormal (<2.5 ms per beat) in 4 patients. Mean TO was abnormal (>0%) in 13 patients. All 4 patients with abnormal TS also had abnormal TO. Examples of VV-interval sequences from patients with low and normal HRT are shown in Figure 1. There were no significant differences between normal and abnormal turbulence parameter patients in clinical arrhythmia, LVEF, MI status, or NYHA class (\( P>0.1 \) for all comparisons). Stratifying TS and TO results by clinical variables (Table 1) showed no significant differences except that mean TO was negative for NYHA classes 0 and 1 and positive for NYHA classes 2 to 4 (\( P<0.01 \)).

Coupling Interval and HRT Parameters in Individual Patients
The relationship between turbulence parameters and coupling interval or compensatory pause as analyzed by linear regression was weak for the majority of patients, and no obvious relationships emerged. For example, the linear regression of TS on the VPC coupling interval for individual patients showed consistently low correlation coefficients (\( r^2 =0.17±0.25 \)), with a slope significantly different from 0 seen in only 3 patients. These 3 patients had negative regression slopes. A search for relationships between TS, TT, or TO and compensatory pause or compensatory pause as analyzed by linear regression was weak for the majority of patients, and no obvious relationships emerged. For example, the linear regression of TS on the VPC coupling interval for individual patients showed consistently low correlation coefficients (\( r^2 =0.17±0.25 \)), with a slope significantly different from 0 seen in only 3 patients. These 3 patients had negative regression slopes. A search for relationships between TS, TT, or TO and compensatory pause or

<table>
<thead>
<tr>
<th>Variable</th>
<th>TS</th>
<th>TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVT</td>
<td>9.8±9.7</td>
<td>−0.4±1.4</td>
</tr>
<tr>
<td>VT</td>
<td>8.5±5.3</td>
<td>−0.04±0.8</td>
</tr>
<tr>
<td>LVEF &gt;0.40</td>
<td>9.4±8.4</td>
<td>−0.5±1.3</td>
</tr>
<tr>
<td>LVEF ≤0.40</td>
<td>9.6±5.8</td>
<td>0.1±0.6</td>
</tr>
<tr>
<td>NYHA 0–1</td>
<td>9.6±8.0</td>
<td>−0.6±1.0</td>
</tr>
<tr>
<td>NYHA 2–4</td>
<td>8.2±5.7</td>
<td>0.6±0.7</td>
</tr>
<tr>
<td>Age &lt;65 y</td>
<td>11.5±8.5</td>
<td>−0.3±1.4</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>7.3±5.3</td>
<td>−0.1±0.7</td>
</tr>
<tr>
<td>No MI</td>
<td>10.0±8.4</td>
<td>−0.4±1.3</td>
</tr>
<tr>
<td>MI</td>
<td>8.4±5.6</td>
<td>0.1±0.6</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*\( P=0.007 \) for comparison. \( P>0.1 \) for all other comparisons.
Regression line and 95% confidence bands are shown. Such statistically significant relationships were rare. Figure 2 shows sample patient graphs from the few individuals who did have significant correlations between their HRT parameters and coupling interval. There was little overlap between the patients expressing significant correlation for one regression and another; ie, it was not the case that the same 3 patients showed significant correlations for all of the 6 linear regression analyses.

Because there were a few patients who did have significant correlations between turbulence parameters and coupling interval/compensatory pause, we hypothesized that correlations might exist in subgroups of patients. We compared the slope values of the regression of turbulence parameters on coupling interval/compensatory pause between mutually exclusive subgroups, namely, between low and high LVEF, between positive and negative history of MI, between the presence and absence of structural heart disease, and between VT and SVT, in the hope that some pattern would emerge that distinguished patients with positive slope from those with negative slope. However, none of these comparisons produced statistically significant differences (P>0.2 for all).

**Population Trends**

Linear regression analysis of TS, TO, and TT on coupling interval and compensatory pause was performed on pooled patient data, for which all data points from all patients (334 data points) were analyzed together. Interestingly, TS was found to be positively correlated with compensatory pause (P=0.0009), and TT was found to be positively correlated with both coupling interval (P=0.0003) and compensatory pause (P=0.0003). However, normalizing the coupling interval or compensatory pause by expressing it as a percentage of the RR interval before the VPC abolished these correlations (values became P=0.27, P=0.50, and P=0.19, respectively). Inspection of the data suggested that the correlations that we saw were in fact due to patients with low heart rates having high TS and early TT values and patients with high heart rates having low TS and late TT values rather than an inherent relationship between turbulence parameters and coupling interval/compensatory pause. This conjecture was confirmed when turbulence parameter values over various coupling intervals for each patient were condensed into mean values and the linear regressions of these mean values versus SCL were analyzed (Figure 3). Patients with higher heart rates (shorter SCLs) did indeed have smaller TS and later TT and vice versa. The linear regression equations were TS=1.1+0.1×SCL (r²=0.046, P=0.28) and TT=8.8 to 0.05×SCL (r²=0.217, P=0.013). Removal from the analysis of the 2 patients with very high TS values improved the correlation between TS and SCL to the level of statistical significance: TS=−2.7+0.01×SCL (r²=0.212, P=0.018). No correlation was found between TO and SCL (TO=−2.2+0.002×SCL [r²=0.012, P=0.57]).

![Figure 2](image-url)  
**Figure 2.** Examples of patients showing significant relationships between TS, TO, and TT (dependent variables) and coupling interval. Such statistically significant relationships were rare. Regression line and 95% confidence bands are shown.

![Figure 3](image-url)  
**Figure 3.** Correlation between the 3 HRT parameters and baseline VV (SCL) interval. Mean TS and mean TO (m TO) value of each of 28 patients is plotted against that patient’s baseline VV. m TT indicates mean TT.

**TABLE 2. Regression of Heart Rate Turbulence Parameters on VPC Coupling Interval and Compensatory Pause**

<table>
<thead>
<tr>
<th>Regression</th>
<th>Patients With Negative Slope, n</th>
<th>Patients With Positive Slope, n</th>
<th>Slope</th>
<th>Correlation Coefficient</th>
<th>Patients With Slope Significantly Different From 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS/CI</td>
<td>18</td>
<td>10</td>
<td>−0.017±0.045</td>
<td>0.17±0.25</td>
<td>3 All negative</td>
</tr>
<tr>
<td>TS/CP</td>
<td>12</td>
<td>16</td>
<td>0.051±0.222</td>
<td>0.15±0.18</td>
<td>3 2 negative</td>
</tr>
<tr>
<td>TO/CI</td>
<td>14</td>
<td>14</td>
<td>−0.0004±0.0043</td>
<td>0.11±0.16</td>
<td>3 All negative</td>
</tr>
<tr>
<td>TO/CP</td>
<td>13</td>
<td>15</td>
<td>−0.002±0.017</td>
<td>0.14±0.16</td>
<td>2 Both positive</td>
</tr>
<tr>
<td>TT/CI</td>
<td>18</td>
<td>10</td>
<td>−0.001±0.016</td>
<td>0.17±0.21</td>
<td>3 All negative</td>
</tr>
<tr>
<td>TT/CP</td>
<td>11</td>
<td>17</td>
<td>0.003±0.020</td>
<td>0.15±0.14</td>
<td>3 2 positive</td>
</tr>
</tbody>
</table>

CI indicates coupling interval; CP, compensatory pause. Values are mean±SD.
The general relationship (Figure 3) shown between baseline heart rate and mean TS and mean TO remained true for subgroups of patients, in patients with or without a history of MI, and in patients with or without low LVEF (<40%). In other words, slow heart rate led to higher mean TS and smaller mean TT regardless of clinical characteristics.

**Relationship Between Coupling Interval, Compensatory Pause, and Arterial Pressure**

Possible mechanisms for the lack of a relationship between coupling interval and turbulence parameters were sought. First, we studied the relationship between coupling interval and compensatory pause. If a compensatory pause is completely compensatory, it should equal approximately twice the VV interval minus the VPC coupling interval; ie, a plot of compensatory pause against the VPC coupling interval should have a slope of −1. Twenty-two of the patients had a slope close to −1 (−1.002±0.303). In 5 of the patients, compensatory pause was not related to the coupling interval; the absolute slope was <0.2. In at least 2 of these patients, V-A conduction was noted, which fixed the compensatory pause value. One patient had an intermediate slope of −0.5.

We next studied the relationship between the VV interval and 3 arterial blood pressure measures (diastolic, systolic, and pulse pressure) in the 10 patients (6 SVT, 4 VT) in whom these were recorded. Figure 4 shows an example from 1 patient that typifies the general relationship seen between the VV interval and arterial pressure. Systolic pressure (open triangles) after a VPC was steeply related to VPC coupling interval (points to the left) except at the shortest coupling interval, where systolic pressure became constant and equal to diastolic pressure because no pulse could be measured. Systolic pressure after the compensatory pause (points to the right) was not related to the compensatory pause and remained constant. Diastolic pressure after the systolic peak (solid circles) was inversely related to the VPC coupling interval and to compensatory pause. Pulse pressure (systolic pressure−diastolic pressure) (open circles) was steeply related to the VPC coupling interval and moderately related to compensatory pause, as expected from its arithmetic relation to systolic and diastolic pressures.

**Discussion**

The first goal of the present study was to assess whether one could measure HRT in the setting of a clinical electrophysiological study. Mainly, we expected heightened sympathetic tone due to the stress of the procedure to mask or exaggerate HRT. For example, it has been shown that reduced heart rate variability (and its implied increased sympathetic activity) is associated with abnormal TO and TS. Although we did not have a control unstressed recording period, we concluded that the clinical electrophysiological setting did not greatly reduce HRT because the majority of the patients whom we studied had at least normal TS (24 of 28 patients). The obvious comparison would have been with the patients’ own Holter recordings; however, they were not available in this referral population.

The second goal of the present study was to assess the effect of the VPC coupling interval on turbulence parameters. We hypothesized that greater hemodynamic perturbation due to a shorter VPC coupling interval would result in a larger turbulence response. Our results were contrary to what we expected. We computed 6 linear regressions: the 3 turbulence parameters (dependent variables) on coupling interval and on compensatory pause (independent variables). Computed for each patient, slopes significantly different from 0 were found in only 2 or 3 of the 28 patients for each of the 6 regressions. The fact that there was little overlap of these patients and that the sign of the regression slope was evenly distributed between positive and negative made it unlikely that a low signal-to-noise ratio was masking a true relationship between coupling interval and turbulence parameters.

When patient data were pooled, TS and TT were positively correlated with coupling interval and compensatory pause. These correlations were found to be due to patients with high baseline heart rates having low TS and late TT and those with low heart rates having high TS and early TT rather than due to a relationship between coupling interval and these parameters. This suggests that turbulence parameter variability in an individual is far less than interindividual variability. However, HRT is not fixed for an individual. We have shown that turbulence parameters can change immediately preceding ventricular tachyarrhythmias in individuals who have normal parameters at baseline recording.

Our negative results were consistent with the results of 2 studies indicating independence between blood pressure values and VV intervals on a beat-to-beat basis. In the first study, arterial blood pressure turbulence was calculated in a manner similar to that used for HRT calculations, and TS was found to be closely correlated with a baroreflex sensitivity measure, whereas arterial pressure turbulence, which one might expect to be even more closely corre-
lated, was not correlated with the baroreflex measure. In the second study, heart rate dynamics in healthy volunteers were studied under various doses of norepinephrine, which increased average arterial blood pressure and average VV intervals. At longer VV intervals, the Poincaré plot of the VV interval data demonstrated the existence of abrupt changes of the VV interval from one beat to the next, whereas the Poincaré plot of the systolic arterial pressure showed that arterial pressure remained constant from one beat to the next.

We sought reasons for the lack of relationship between the VPC coupling interval and turbulence parameters. There were roughly 4 possibilities corresponding to nonlinearity or weak correlation at steps connecting VPC to HRT (Figure 5). First, the blood pressure after a VPC and VPC coupling interval was considered (arrow 1). In the 10 patients for whom we obtained blood pressure measurements, we found that all blood pressure measures were linearly related to the coupling interval (example in Figure 4, left), excluding this possibility. Our result was consistent with the study in which increasing prematurity of the VPC coupling interval caused increasing burst amplitude of sympathetic nerve activity in the peroneal nerve. Blood pressure in several of the patients reached a plateau at the shortest coupling intervals, similar to nerve activity in that study.

We next considered the compensatory pause–VPC coupling interval relationship (Figure 5, arrow 2). For example, in the subgroup analysis, compensatory pause was poorly but consistently better correlated with turbulence parameters than was the coupling interval. However, we found that compensatory pause was fully compensatory (ie, linearly related to coupling interval) in 21 of 28 patients. Furthermore, removal of the 5 patients with flat compensatory pauses from analyses did not improve correlations between the coupling interval and turbulence parameters. This result, coupled with the fact that turbulence parameters correlated poorly even with compensatory pause, makes this explanation unlikely.

We also considered the compensatory pause–arterial pressure relationship (Figure 5, arrow 3). We found that systolic pressure after the compensatory pause was constant and independent of compensatory pause value. If systolic pressure rather than diastolic or pulse pressure is the major determinant of turbulence parameter values, it could explain the lack of correlation between coupling interval and turbulence parameters. Finally, HRT itself is unlikely to be a linear function of arterial pressure values because of the intervening baroreflex arc (Figure 5, arrow 4). In summary, the poor correlation between coupling interval and turbulence parameters is likely to be due to flat systolic arterial pressure after the compensatory pause (Figure 5, arrow 3) or because of nonlinearity in the baroreflex arc (Figure 5, arrow 4).

Possible Limitations
Half of the patients in the present study were on β-blockers. A recent mathematical modeling study indicated that β-blockade reduces TS. However, only 4 of the 28 patients in the present study had abnormally low TS. Furthermore, another study showed that both TS and TO were independent predictors of mortality in a post-MI population even in patients taking β-blockers, for whom predictive values of other noninvasive measures failed. The results can be reconciled if TS is reduced somewhat by β-blockers but not enough to shift TS below 2.5 into abnormal values.

Nineteen patients received sedative medications during the present study. However, we note that others have found minimal electrophysiological effects of these medications when they are used to achieve higher levels of sedation than we sought. In addition, SCL and turbulence parameters were not statistically different between those receiving sedatives and those that did not.

Suggested Protocol
Because turbulence parameters do not seem to be heavily dependent on the coupling interval, we suggest for future studies that induced HRT values be computed from averaging the results of 10 extrastimuli given with a spacing minimum of 20 sinus beats, at a coupling interval that is 60% to 70% of SCL. The mean normalized coupling interval of all extrastimuli given was 63.7±15.2% in the present study. In another study, we had consistent capture with the use of a 60% coupling interval and no VT induction.

Conclusions
It seems that turbulence parameters can be easily obtained as part of an electrophysiological study and may provide electrophysiological studies with risk-stratifying information beyond VT inducibility. Turbulence parameters do not vary significantly with VPC coupling interval or compensatory pause, suggesting that a short VPC coupling interval is not required for accurate or better measurement of induced HRT.

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References
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