Symbolic Dynamics of Heart Rate Variability
A Probe to Investigate Cardiac Autonomic Modulation

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Background—Sympathetic and parasympathetic systems are considered the principal rapidly reacting systems that control heart rate.

Methods and Results—We propose a symbolic analysis series to quantify the prevalence of sympathetic or parasympathetic cardiac modulation. This analysis decomposes the heart rate variability series in patterns lasting 3 beats and classifies them into 3 categories: nonvariable, variable, and very variable patterns referred to as 0V, 1V, and 2V patterns. First, we applied this method to experimental and pharmacological conditions characterized by sympathetic activation (tilt test, handgrip, nitroprusside, and high-dose atropine administration) or parasympathetic activation (phenylephrine and low-dose atropine administration) in 60 healthy subjects. An increase in sympathetic modulation and a vagal withdrawal elicited a significant increase in 0V patterns and a decrease in 2V patterns, whereas parasympathetic dominance induced the opposite, reflecting a reciprocal sympathovagal balance. The second part of the study considered a series of 300 beats before the onset of major arrhythmic events in patients with an implantable cardioverter-defibrillator. Symbolic analysis detected an increase in the percentage of 0V patterns before the onset of major arrhythmias compared with baseline (41.6±3.9% and 24.4±2.9%, respectively; P<0.01), indicating a sympathetic prevalence. On the other hand, the 2V patterns did not decrease before major arrhythmias, suggesting the presence of nonreciprocal autonomic modulations.

Conclusions—Symbolic analysis of 3 beat sequences takes into account the different time course of sympathetic and parasympathetic cardiac modulations and seems appropriate for elucidating the neural pathophysiological mechanisms occurring during the short periods that precede acute cardiac events. (Circulation. 2005;112:465-470.)

Key Words: arrhythmia • heart rate • nervous system, autonomic

The autonomic nervous system is able to change cardiac beat-to-beat interval length in response to several perturbations. The sympathetic and parasympathetic systems are considered the principal rapidly reacting systems that control heart rate. The 2 systems have different latent periods and different time courses; sympathetic effects on heart rate are much slower than parasympathetic. Linear analysis of heart rate variability (HRV) can furnish noninvasive indexes of cardiac autonomic modulation in the presence of rhythmic variability. In settings characterized by rapid and nonrepetitive changes, like the periods preceding cardiac events, noninvasive standard measurements of these control systems give less reliable information than during more stable periods.

The aim of the present study was to test the ability of a nonlinear tool based on symbolic analysis of 3-beat sequences to distinguish sympathetic and parasympathetic cardiac modulation. First, a specific protocol modifying the activity of the 2 branches of the autonomic nervous system was used to verify this method. Second, this technique was then applied to evaluate the role of the autonomic system before the onset of major arrhythmias, because sympathetic activation is considered one of the factors implicated in life-threatening arrhythmias. The symbolic analysis method adopted consists mainly of the transformation of a time series (RR intervals) into short patterns (3 beats long), their classification, and the evaluation of their rates of occurrence. This type of nonlinear analysis takes into account short patterns distributed in the RR series and would seem appropriate for studying the short HRV instabilities that precede sudden cardiac events such as major arrhythmias. Although previous studies proposed other nonlinear algorithms to stratify arrhythmic risk in cardiac patients, our method provides new interpretative insights into the role played by autonomic modulation in triggering major arrhythmic events.
Methods

Autonomic Tests
Sixty healthy subjects (40 men, 20 women) were studied in experimental and pharmacological conditions characterized by different autonomic modulations. Mean age was 34±2 years (range, 22 to 71 years); mean systolic and diastolic blood pressures were 118±3 and 72±2 mm Hg. None of the subjects were on any medications, and all subjects had normal physical examination, normal resting ECG, and normal effort tolerance. These healthy subjects were studied first at rest in comfortable stable conditions. Three hundred beats were recorded at rest after 15 minutes of acclimatization. Subsequently, in 43 subjects, the ECG recording was continued during passive tilt (80°); 300 beats were continuously recorded after 3 minutes from start of tilt. In 10, a period of 300 beats during handgrip at 30% of their maximum hand strain was also recorded. Moreover, 10 young subjects received low (2 μg/kg) and high (15 μg/kg) bolus doses of atropine. Their recordings of 300 beats started 5 minutes after the bolus of atropine. Seven additional young subjects received 1 μg·kg⁻¹·min⁻¹ infusion of phenylephrine and 1.2 μg·kg⁻¹·min⁻¹ IV infusion of nitroprusside. The recordings started 3 minutes after the beginning of each drug administration. The local ethics committee approved the study. All subjects gave written informed consent.

Patients With an Implantable Cardioverter-Defibrillator
We collected 28 series of 300 RR periods (intervals between 2 RR waves of intracavitary ECG recordings) preceding ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with an implantable cardioverter-defibrillator (ICD; Medtronic Inc). The RR series were automatically stored in the device when an arrhythmic event required an internal DC shock. The intracavitary ECG was sampled at 100 Hz; up to 1000 beats were collected before each episode. The 300 beats before the onset of major arrhythmias were analyzed. All enrolled patients had experienced previous episodes of major arrhythmia before ICD implantation.

The 20 men and 8 women had a mean age of 53±3 years (range, 25 to 73 years). None of the patients were receiving β-blockers at the time of recordings. Three patients were on amiodarone therapy; no other antiarrhythmic drugs were being used.

The results were compared with control time series collected at rest in the same patients during the periodic ICD check (the last 300 beats recorded up to 2000 beats).

Of 28 consecutive series, 21 were considered for the analysis: 7 were excluded for the following reasons: 2 for atrial fibrillation, 3 for >10% of arrhythmic beats, and 2 for a pacemaker-driven rhythm. In the presence of ectopic beats (<10%), HRV series was linearly interpolated between the preceding/successive normal RR intervals.

Symbolic Dynamics
The method was fully described and validated previously. Briefly, RR interval sequences of length L = 300 were selected. The length (L) was kept fixed in all analyses. The full range of the sequences was uniformly spread on 6 levels (from 0 to 5); each level was expressed in absolute (ms²) and normalized units and as the percentage of 0V and 2V patterns before major arrhythmic events and during control periods were tested with a 2-tailed paired Student t test or the Wilcoxon signed-rank test when the data were not normally distributed (SigmaStat for Windows, version 2.03). One-way ANOVA for repeated measures and Dunnett’s method for multiple comparisons were used to compare the different experimental and pharmacological conditions with resting state in healthy subjects. If the data were not normally distributed, the Friedman rank test for multiple comparisons

Spectral Analysis
Frequency domain analysis of HRV was performed with an autoregressive algorithm on the same sequences used for symbolic dynamics. Briefly, the power spectral density was calculated for each RR series. Three spectral components were considered: very low frequency, from 0 to 0.03 Hz; low frequency, from 0.03 to 0.15 Hz; and high frequency, from 0.15 to 0.40 Hz. The spectral components were expressed in absolute (ms²) and normalized units and as the ratio of low to high frequency. Normalization consisted of dividing the power of a given spectral component by the total power minus the power below 0.03 Hz and multiplying the ratio by 100.

Statistical Analysis
Data are presented as mean±SE. The differences in percentage of 0V and 2V patterns before major arrhythmic events and during control periods were tested with a 2-tailed paired Student t test or the Wilcoxon signed-rank test when the data were not normally distributed (SigmaStat for Windows, version 2.03). One-way ANOVA for repeated measures and Dunnett’s method for multiple comparisons were used to compare the different experimental and pharmacological conditions with resting state in healthy subjects. If the data were not normally distributed, the Friedman rank test for multiple comparisons

Figure 1. Synthetic illustration of symbolic analysis method. RR series was uniformly spread on 6 levels (from 0 to 5); each level was identified by symbol (number), and patterns of length of 3 symbols were constructed.
was used. Correlation values \( r \) were assessed by the Pearson \( \chi^2 \) test statistic. A value of \( P<0.05 \) was considered statistically significant.

**Results**

**Autonomic Tests**

In healthy people, a significant increase in 0V dynamics was detectable during tilt and handgrip, conditions characterized by an increased sympathetic modulation and vagal withdrawal (Figure 3, top left); in contrast, in these experimental conditions, the percentage of 2V dynamics was significantly decreased (Figure 3, top right).

After high-dose atropine (parasympathetic blockade), a significant increase in 0V patterns and a decrease in 2V patterns were detectable, whereas low-dose atropine (parasympathetic agonist effect) produced no significant changes (Figure 3, middle).

The infusion of phenylephrine (reflex increase of cardiac parasympathetic modulation) determined a significant increase in 2V percentage, whereas nitroprusside infusion (reflex increase in cardiac sympathetic modulation) caused a significant increase in 0V dynamics (Figure 3, bottom). The changes in 1V patterns did not achieve the threshold of significance during autonomic tests. The results of Shannon entropy analysis in healthy subjects are shown in Figure 4.

In Table 1, the results of time and frequency domain analyses of the same series (300 beats) during the different physiological and pharmacological experimental conditions are reported as differences from resting conditions. The correlations between 0V or 2V patterns and mean RR or spectral components during tilt test, which represented the more numerous experimental condition (43 subjects), did not reach statistical significance.

**Patients With an ICD**

In 17 of 21 patients, the percentage of nonvariable symbolic patterns (3 beats on the same level; 0V) increased before life-threatening arrhythmias compared with baseline (0V patterns at baseline, 24.4±2.9%; before the onset of VT/VF, 41.6±3.9%; \( P<0.01 \); Figure 5, top); on the other hand, the small increase in 2V patterns did not reach statistical significance (2V patterns at baseline, 3.2±1.0%; \( P=0.14 \); Figure 5, middle). Noteworthy, the percentages of both 0V and 2V patterns were substantially unchanged in the RR surrogate series at baseline and before the onset of major arrhythmias (0V patterns, 24.4±3.4% and 29.6±3.9%; 2V patterns, 3.0±1.0% and 2.5±1.1%, respectively). The percentage of 1V patterns was not significantly reduced before arrhythmic events compared with baseline. Shannon entropy, a measure of complexity, was significantly reduced in periods preceding major arrhythmias compared with control periods (3.19±0.08 and 3.59±0.07, respectively; \( P<0.05 \); Figure 5 bottom). Finally, heart rate increased in periods preceding major arrhythmia,
whereas variance and spectral components did not change substantially (Table 2), even when the powers are expressed in a logarithmic scale. The increase in heart rate was correlated with the increase in 0V patterns before the onset of major arrhythmias ($r=0.70; P<0.01$). Moreover, a slight but significant positive correlation was found between high frequency (in ms$^2$), as well as in logarithmic scale and the percentage of 2V patterns before arrhythmias ($r=0.43$, $P<0.05$; and $r=0.54$, $P<0.05$, respectively).

**Discussion**

In the clinical setting, sudden death resulting from cardiac arrhythmias is an important cause of mortality.$^{14}$ The onset of major arrhythmias is generally considered an unpredictable phenomenon. Common cardiovascular risk factors can help to identify subjects at high risk of arrhythmias, but the precise instant of arrhythmias onset is considered erratic.$^{15}$ Coronary artery disease is present in 80% of subjects who experience major arrhythmias,$^{16}$ and previous studies suggest that transient or nontransient cardiac ischemic events are triggers for arrhythmic episodes.$^{17}$ Nevertheless, not all ischemic events lead to life-threatening arrhythmias. Additional factors triggering major arrhythmias have been proposed. Among them, increased sympathetic modulation seems to play a crucial role.$^{18,19}$ In experimental animal models, the infusion of catecholamines after coronary occlusion induced ventricular arrhythmias.$^{20}$ The standard linear HRV methods of analysis do not seem adequate to study any short-term instability that may precede major arrhythmias,$^{21}$ probably because of the presence of only brief and transient instabilities in the RR interval dynamics,$^{22}$ thus leading to controversial results.$^{21,23,24}$

We proposed a nonlinear method of HRV analysis (3-beat symbolic analysis) to quantify the prevalence of sympathetic or parasympathetic cardiac modulation in conditions in which the use of a linear HRV approach$^6$ is limited or even disputable. The method was validated by experimental and pharmacological protocols characterized by specific changes in sympathovagal balance. In these experimental conditions, the percentage of symbolic patterns changed in clear directions, consistent with expected changes in sympathetic or vagal cardiac modulation. Specifically, an increase in sympathetic modulation and vagal withdrawal elicited both an increase in 0V patterns and a decrease in 2V patterns, whereas parasympathetic prevalence induced opposite changes: an increase in 2V patterns and a decrease in 0V patterns. Our method of analysis was able to take into account short instabilities in the HRV series that may provide insights into autonomic cardiac regulation, considering the different latencies and time courses of the fast parasympathetic and slow sympathetic modulations.$^{1-3}$

Wessel et al.$^{25}$ recently showed, using a symbolic method based on a “word” of 6 symbols, that symbolic dynamics of RR series forecasted life-threatening arrhythmias. Shusterman et al.$^{26}$ recognized disturbances in “core” patterns, indicating progressive destabilization of cardiac rhythm, which would predict the onset of spontaneous sustained ventricular tachyarrhythmias. In our patients with ICDs, the period before the onset of major arrhythmias was characterized by an increase in flat symbolic (0V) patterns, suggesting that a sympathetic prevalence could facilitate the onset of these arrhythmias. Although an increase in 0V patterns was associated with a decrease in 2V patterns during

**TABLE 1. Changes From Rest Induced by Autonomic Tests in Healthy People**

<table>
<thead>
<tr>
<th>Change in Tilt</th>
<th>Change in Handgrip</th>
<th>Change in Atropine 1</th>
<th>Change in Atropine 2</th>
<th>Change in Phenytoin</th>
<th>Change in Nitropusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (ms)</td>
<td>144±25*</td>
<td>54±24</td>
<td>80±20†</td>
<td>437±41†</td>
<td>128±31*</td>
</tr>
<tr>
<td>VAR (ms²)</td>
<td>401±376</td>
<td>144±295</td>
<td>212±724</td>
<td>3925±961</td>
<td>2978±1585</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>618±240</td>
<td>507±273</td>
<td>514±573</td>
<td>2242±749</td>
<td>717±654</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>354±3.5†</td>
<td>22.7±6.5†</td>
<td>11.8±7.6</td>
<td>14.2±14.2</td>
<td>12.1±5.9</td>
</tr>
<tr>
<td>HF (μV)</td>
<td>979±245</td>
<td>97±76</td>
<td>330±501</td>
<td>1568±571</td>
<td>812±1044</td>
</tr>
<tr>
<td>LF/HF</td>
<td>33.1±3.5†</td>
<td>21.6±6.6*</td>
<td>12.3±7.2</td>
<td>16.8±11.7</td>
<td>13.0±5.3</td>
</tr>
<tr>
<td>LF (μV)</td>
<td>10.21±1.82†</td>
<td>3.31±1.07*</td>
<td>3.61±2.62</td>
<td>11.37±5.92</td>
<td>1.67±0.73</td>
</tr>
</tbody>
</table>

**Abbreviations as in Figure 3. **P<0.05; †P<0.01.

$^*$Value during tests is significantly different from value at rest ($P<0.05$).

$^†$P<0.01.
experimental and pharmacological tests in healthy subjects, the significant increase in 0V before the onset of major arrhythmias was not coupled with a decrease in 2V patterns in ICD patients. The possible concomitance of both vagal and sympathetic actions, most likely on a reflex basis, could facilitate arrhythmias by a complex interplay.27 Symbolic analysis seems able to detect the coexistent excitation of the 2 systems, weakening the concept that vagal and sympathetic outflows in pathophysiological conditions work exclusively in a sort of reciprocal arrangement. Alternatively, a trend to increased 2V patterns may be due to nonautonomic mechanisms affecting heart rate dynamics and resulting from alternating patterns of RR intervals.28 Moreover, electric alternation of ST segment and T wave has been previously described to precede the VT/VF events.29 Inhomogeneity of ventricular repolarization might explain both RR and repolarization alternating patterns,30 which, in turn, might be facilitated by sympathetic stimulation.31

Other nonlinear approaches such as Shannon entropy, which clearly decreased before the onset of arrhythmic events, were less able than symbolic dynamics to identify the experimental changes in cardiac autonomic modulation. Finally, we stress the simplicity of the method used for symbolic analysis. In a previous study,8 we verified that 6 levels for a sequence of 3 beats is the most appropriate compromise to best detect the relative changes induced by the autonomic modulation on HRV. The presence of ectopic beats influences the results of classification by reducing the number of different patterns (ie, complexity). Therefore, the application of a proper correction procedure is mandatory in the presence of ectopic beats.

Study Limitations
We compared recordings preceding the onset of major arrhythmias with basal recordings obtained at rest with the same device during a periodic ICD check. Consequently, we have no data to assess whether sympathetic activation is greater before a major arrhythmic event compared with other periods throughout the day, particularly during activity. Moreover, our symbolic analysis is based on normal functioning of the SA node and does not provide a measure of repolarization properties of myocardial substrate, which is directly involved in the genesis of life-threatening ventricular arrhythmias.

Conclusions
As shown in the first part of the study (autonomic tests), an increase in sympathetic cardiac modulation determines the rise in 0V and the decrease in 2V patterns, whereas opposite results are observed during an increase in parasympathetic cardiac modulation. Reciprocal changes are observed in the normalized power of low- and high-frequency spectral components of HRV. As reported in the second part of the study, before the onset of major arrhythmias, the symbolic pattern possibly related to prevalent sympathetic modulation increases, and the pattern possibly related to vagal modulation

### Table 2. HRV Indexes in Basal Condition and Before the Onset of VF and VT in 21 Patients With an ICD

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Before VF/VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, ms</td>
<td>891±41</td>
<td>767±43*</td>
</tr>
<tr>
<td>VAR, ms²</td>
<td>1328±352</td>
<td>1354±4455</td>
</tr>
<tr>
<td>VLF, ms²</td>
<td>889±293</td>
<td>1004±423</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>311±100</td>
<td>260±90</td>
</tr>
<tr>
<td>LF, NU</td>
<td>60.0±6.5</td>
<td>53.7±6.6</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>100±22</td>
<td>59±16</td>
</tr>
<tr>
<td>HF, NU</td>
<td>33.8±6.2</td>
<td>26.4±4.1</td>
</tr>
<tr>
<td>LF/HF</td>
<td>10.97±3.61</td>
<td>7.43±3.61</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Values are expressed as mean±SE.

*Value in basal condition significantly different (P<0.05) from value before the onset of VF/VT.
does not decrease in a reciprocal way. Standard HRV analysis does not detect any significant change in these conditions.

References


CLINICAL PERSPECTIVE

Analysis of heart rate variability (HRV) provides an indication of sympathetic and vagal activity that has provided pathophysiological, clinical, and prognostic relevance to heart disease. Although power spectrum analysis is a powerful tool for assessing HRV, it requires a stable signal series, and the analysis is involved. A simple symbolic analysis is proposed that is based on 3-beat periods to quantify HRV. For initial validation, it was first shown to respond to physiological stimuli that induce changes in autonomic tone. It was also compared with HRV changes detected by power spectrum analysis. Subsequently symbolic analysis was applied to the ECG recordings obtained from ICDs in patients who had episodes of ventricular arrhythmias. This new approach detected signs of sympathetic overactivity preceding these major arrhythmic events. Interestingly, the symbolic analysis suggested that the increased sympathetic activity was not accompanied by decreased vagal modulation, in contrast to the expected sympathovagal relationship in physiological conditions. Symbolic analysis seems to overcome some limitations of other power spectrum analysis of HRV. Using this analysis to predict arrhythmic events may allow development of a tailored therapy approach to preventing arrhythmias.
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In the article “Symbolic Dynamics of Heart Rate Variability: A Probe to Investigate Cardiac Autonomic Modulation” by Guzzetti et al, which appeared in the July 26, 2005, issue of the journal (Circulation. 2005;112:465–470), the ninth author’s name was misspelled. The proper spelling is “Alberto Malliani, MD.”

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