Altered Complexity and Correlation Properties of R-R Interval Dynamics Before the Spontaneous Onset of Paroxysmal Atrial Fibrillation

Saila Vikman, MD; Timo H. Mäkikallio, MD; Sinikka Yli-Mäyry, MD; Sirkku Pikkuja, MD; Anna-Maija Koivisto, BSc; Pekka Reinikainen, MD; K.E. Juhani Airaksinen, MD; Heikki V. Huikuri, MD

Background—Trigger mechanisms for the onset of paroxysmal atrial fibrillation (AF) in patients without structural heart disease are not well established. New analysis methods of heart rate (HR) variability based on nonlinear system theory may reveal features and abnormalities in R-R interval behavior that are not detectable by traditional analysis methods. The purpose of this study was to reveal possible alterations in the dynamics of R-R intervals before the spontaneous onset of paroxysmal AF.

Methods and Results—Traditional time and frequency domain HR variability indices, along with the short-term scaling exponent $a_1$ and approximate entropy (ApEn), were analyzed in 20-minute intervals before 92 episodes of spontaneous, paroxysmal AF in 22 patients without structural heart disease. Traditional HR variability measures showed no significant changes before the onset of AF. A progressive decrease occurred both in ApEn ($1.09 \pm 0.26$ 120 to 100 minutes before AF; $0.88 \pm 0.24$ 20 to 0 minutes before AF; $P < 0.001$) and in $a_1$ ($1.01 \pm 0.28$ 120 to 100 minutes before AF, $0.89 \pm 0.28$ 20 to 0 minutes before AF; $P < 0.05$) before the AF episodes. Both ApEn ($0.89 \pm 0.27$ versus $1.02 \pm 0.30$; $P < 0.05$) and $a_1$ ($0.91 \pm 0.28$ versus $1.27 \pm 0.21$; $P < 0.001$) were also lower before the onset of AF compared with values obtained from matched healthy control subjects.

Conclusions—A decrease in the complexity of R-R intervals and altered fractal properties in short-term R-R interval dynamics precede the spontaneous onset of AF in patients with no structural heart disease. Further studies are needed to determine the physiological correlates of these new, nonlinear HR variability measures. (Circulation. 1999;100:2079-2084.)

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

Analysis of heart rate (HR) variability has become an important, noninvasive tool for assessing cardiac autonomic regulation. Conventionally, nonspectral and spectral analyses of HR variability have been used to measure R-R interval variability. A number of new methods based on nonlinear system theory have recently been developed to give more insight into complex HR dynamics. These methods may reveal subtle abnormalities in cardiac autonomic regulation that may not be uncovered by traditional measures of HR variability. These new methods have already provided clinically important information on abnormalities in HR behavior in various clinical settings.

The autonomic nervous system may play an important role as a trigger for the spontaneous onset of paroxysmal atrial fibrillation (AF). However, only a few and partly controversial reports exist concerning changes in HR variability preceding the onset of AF. A recent study suggested that altered complexity of R-R interval dynamics precedes the AF episodes of patients after coronary artery bypass graft surgery. The trigger mechanisms and pathophysiology of AF may be different between patients with and without organic heart disease and in various clinical situations. The present study was designed to test the hypothesis that altered R-R interval dynamics, as analyzed by new complexity and fractal measures, may also precede the onset of paroxysmal, idiopathic AF.

Methods

Patients

The 24-hour ECG recordings of patients who had paroxysmal episodes of AF, who had no structural heart disease, and who were studied at Tampere and Oulu University hospitals in Finland were...
prospectively collected from 1991 to 1998 from patients who underwent clinically indicated ECG recordings. Only recordings containing ≥1 paroxysmal AF episode(s) lasting >10 seconds, with at least 20 minutes of sinus rhythm preceding the AF, were included in the analyses. Patients with structural heart disease, hypertension, diabetes, sick sinus syndrome, or atrioventricular accessory pathways were excluded from the study. Patients >60 years of age who had sinus pauses >2.5 seconds were also excluded.

The study population consisted of 22 patients, for whom 26 ECG recordings (24-hour) containing 92 episodes of paroxysmal AF were made. The clinical characteristics of the patients are shown in Table 1. An age- and sex-matched healthy control group of subjects who had no evidence of organic heart disease and no history of AF was selected from among individuals who were participating in a larger trial comparing the characteristics of hypertensive and normotensive subjects; the latter group was randomly selected from the general population of Oulu using their social security numbers. All control patients had undergone a complete physical examination and had a medical history that revealed no cardiovascular disease or medication. They all had normal blood pressure. All underwent 12-lead ECG; M-mode, 2D, and Doppler echocardiography; and a 2-hour glucose tolerance test. None had evidence of ischemic ST-segment depression in exercise ECG. The test protocol was approved by the Ethics Committee of the University of Oulu.

Table: Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Age, y</th>
<th>52±11 (range, 28–70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>11/11</td>
</tr>
<tr>
<td>Cardiac medication during recording</td>
<td>(n=26)</td>
</tr>
<tr>
<td>β-Blocking agents</td>
<td>11/26 (42.3%)</td>
</tr>
<tr>
<td>Digitals</td>
<td>3/26 (11.5%)</td>
</tr>
<tr>
<td>Type IA antiarrhythmics</td>
<td>2/26 (7.7%)</td>
</tr>
<tr>
<td>Type IC antiarrhythmics</td>
<td>5/26 (19.2%)</td>
</tr>
<tr>
<td>No medication</td>
<td>13/26 (50%)</td>
</tr>
</tbody>
</table>

Analysis of HR Variability

After the ECG data were transferred to the microcomputer, the R-R interval series was edited automatically; after this, manual editing was also performed to delete all premature beats and noise. All questionable portions were compared with 2-channel Holter ECGs. Only segments with >80% qualified sinus beats were included. Details of this analysis and filtering method have been described previously. Analysis of HR variability was performed on 6 sequential, 20-minute intervals starting 120 minutes before the onset of AF. From 1:1 matched control subjects, the HR variability measures were analyzed in one 20-minute interval at the same time of day as the AF patients’ last 20-minute period before AF onset. All analyses of R-R interval variability were performed with a custom-made analysis program (Hearts, Heart Signal Co), and the details of the methods have been described elsewhere.

Twenty-minute R-R interval data were then divided into 2 segments of equal size according to their beat count; a linear detrend was applied to those segments of 400 to 1000 samples to make the data more stationary. An R-R interval spectrum was computed over the 20-minute periods according to a previously described method. A fast Fourier transform method was used to estimate the power-spectrum densities of HR variability. The power spectra were quantified by measuring the area in 2 frequency bands: 0.04 to 0.15 Hz (low frequency [LF]) and 0.15 to 0.40 Hz (high frequency [HF]). The ratio between LF and HF spectra was also calculated. The SD of the normal R-R intervals and the mean length of the R-R intervals in 20-minute segments were used as time-domain measures of HR variability.

Nonlinear Analysis of R-R Data

The same pre-edited R-R interval time series that was used for the spectral and time domain analyses of HR variability were also used for calculating approximate entropy (ApEn) and for detrended fluctuation analysis. ApEn measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in the subsequent incremental comparisons. A time series containing many repetitive patterns has a relatively small ApEn; conversely, more random data produce higher values. Details of this method have been described previously. Two input values, m and r, must be fixed to compute ApEn; m=2 and r=20% of the SD of the data sets were chosen on the basis of previous findings of good statistical validity. A detrended fluctuation analysis technique was used to quantify the fractal correlation properties of the R-R interval data. This method is a modified root mean square analysis of a random walk. In the present study, we used the scaling exponent α, which measures the strength of the short time (<11 beats) correlation properties of R-R interval data. The details of this method have been described previously. Analyses of ApEn and α were also carried out from data in which only noise was abolished and ectopic beats were not excluded. In the final analysis, both edited and unedited data were used.

Effects of Premature Beats

The amount of ectopic beats by percentage in each 20-minute segment was also analyzed. Because of the potential effect of premature beats on ApEn and scaling exponents, the effect of the premature beats on ApEn and α was assessed by various experiments with real and artificial R-R signals. Short and long time intervals resembling premature beats with a compensatory pause were added, and the amount of replaced beats was increased progressively. First, premature beats with a constant coupling interval (500 ms) were added. The amount of replaced beats was increased progressively from 0% to 40%. Then, the same procedure was repeated, but the time length of coupling intervals was changed randomly within certain limits (350 to 800 ms). The tests were performed on real R-R interval data from a healthy subject with a mean HR of ~60 min, and an SD of RR intervals of 130 ms; they were also performed on artificial signals with 1/f signal properties, a mean R-R interval length of 1000 ms, and an SD of 160 ms.

Statistical Methods

Normal gaussian distribution of the data were verified by the Kolmogorov-Smirnov goodness-of-fit test. Whenever the data were not normally distributed (p>1.0), a logarithmic transformation was performed for all spectral components of HR variability before the statistical analysis. To evaluate whether a significant change occurred in different HR variability measures or in the amount of ectopic beats before the onset of AF, linear mixed models were used. With these models, it is possible to analyze unbalanced repeated-measure designs that use different types of mean and covariance structures. Linear mixed models were fitted using PROC MIXED in the SAS System for Windows (version 6.12). Student’s t test was used to analyze differences between the healthy subjects and patients with AF. P<0.05 was considered significant.

Results

The clinical characteristics of the study population are presented in Table 1. The mean duration of the 92 AF episodes was 22 min, 41 s (median, 38 s; range, 10 s to 6 h, 2 min, 16 s).
Changes in HR Variability Measures and the Amount of Ectopic Beats Before the Onset of AF

Table 2 presents HR variability measures and the amount of ectopic beats in different time periods. None of the traditional time or frequency domain measures showed significant changes before the onset of AF. The amount of ectopic beats increased during the last 40-minute period before the start of AF. ApEn analyzed from fully edited data decreased before the onset of AF (Table 2). When ApEn was analyzed from the real R-R interval data without excluding the ectopic beats, an even more prominent reduction was observed in the complexity of R-R interval dynamics before the onset of AF (Figure). $\alpha_1$ also decreased progressively before the onset of AF when analyzed from data including the premature beats. When all ectopic beats were abolished, $\alpha_1$ showed no significant change before the onset of AF (Table 2).

When the same analyses were performed in a subgroup of patients ($n=11$) who had no medication during a Holter recording, a similar decrease before the onset of AF ($n=33$) was seen in ApEn values, both from fully edited data and from unedited data (Table 3). Also, $\alpha_1$ from unedited data showed a decreasing trend (Table 3). None of the time or frequency domain measures showed any significant change before AF in patients without medication.

Comparison of Nonlinear Measures of HR Dynamics Between Nonmedicated Patients With AF and Healthy Controls

Both ApEn and $\alpha_1$ were significantly lower in the AF patients than in healthy controls when analyzed from the identical 20-minute segments from the unedited R-R intervals. The short-term scaling exponent was also lower in AF patients when analyzed from pure sinus beats (Table 4).

The Effect of Added Ectopic Beats on ApEn and Fractal Scaling Exponent in Real and Artificial Data

ApEn decreased progressively when the amount of premature beats with a constant coupling interval increased. A paradoxical increase was observed when a very small amount of ectopic beats was added. The opposite effect and increasing values of ApEn were observed when the coupling interval time varied randomly between 350 and 800 ms. $\alpha_1$ clearly decreased when ectopic beats, either with fixed or variable coupling intervals, were added to the data (Table 5). The results were almost identical with real and artificial data, but the amount of ectopic beats required to cause a reduction in ApEn was higher with artificial data.

Discussion

The main finding of this study is that altered HR dynamics precede the spontaneous onset of paroxysmal AF episodes in subjects who have no evidence of structural heart disease. These abnormalities in HR dynamics were not detectable by traditional time and frequency domain methods, but they were uncovered by a method describing the complexity and predictability of HR behavior.

Complexity and Correlation Properties of HR Dynamics Before AF

Analysis methods derived from nonlinear dynamics have opened a new approach for studying and understanding the
characteristics of HR behavior. These analysis methods differ from the traditional measures of HR variability because they are not designed to assess the magnitude of variability. Notably, only a weak correlation exists between the new nonlinear measures and traditional measures of HR variability, showing that these new indices describe features of HR behavior that are not detectable by conventional methods. Methods analyzing the complexity (ApEn) and fractal-like correlation properties of HR behavior have been most commonly used to detect abnormalities in R-R interval dynamics.6–10

A stepwise, linear reduction in ApEn values analyzed from 20-minute time periods was the most uniform and consistent finding before the onset of AF episodes. ApEn is a measure that quantifies the regularity and predictability of time series data. Reduced ApEn indicates larger predictability in HR behavior and increased repeatability of the patterns of R-R intervals. ApEn values ≠ 1.0 have been previously described in healthy human heartbeat dynamics. Reduced complexity in HR dynamics has been previously found in various cardiovascular disorders,19,27,28 during bed rest,29 and in normal aging.26 Concurrent with the present observations, a recent study also reported on reduced ApEn preceding spontaneous AF episodes in patients after coronary artery bypass surgery.10 These results suggest that a reduced complexity of R-R interval dynamics is a common finding preceding the onset of AF episodes, independent of the clinical condition and cause of an underlying structural heart disease.

Reduced ApEn was observed here before the AF episodes also when only pure sinus beats were included in the analysis. Ectopic beats with a fixed coupling interval resulted in further reduction in ApEn values, both in tests with artificial signals and in real R-R interval data, resulting in a marked reduction of ApEn before the onset of AF. However, in a large proportion of cases, AF was not preceded by an increase in the frequency of atrial ectopic beats, showing that ectopy itself may not serve as the only trigger of paroxysmal AF.

The short-term scaling exponent α1 also showed a tendency toward lower values before the onset of AF. α1 quantifies the correlation properties of short-term HR dynamics. Consistent with previous findings, α1 values were significantly lower when ectopic beats were left in the data when compared with values from fully edited data, but no change was observed in α1 values in pure sinus interval data. A similar reduction in short-term correlation properties has been reported to precede ventricular fibrillation in postinfarction patients, but the abnormalities in the scaling exponent were more prominent before the onset of ventricular fibrillation than preceding AF.

### Traditional Measures of HR Variability Before AF
Increased sympathetic activity is characterized by a shift of the LF-HF balance in favor of the LF component; the opposite shift in favor of the HF component occurs during vagal tone. Both LF and HF components showed a tendency toward reduced values before AF, but the LF/HF ratio remained unchanged. Consistent with the present findings, in a previous study, only a minority of AF episodes could have been categorized as being induced either by vagal or sympathetic influence.

Nonstationarity of the data and the replacement of ectopic beats by artificial R-R intervals are the major problems in the spectral analysis of HR variability during uncontrolled conditions. These analysis techniques may not be able to detect the subtle abnormalities in cardiovascular autonomic regulation that occur in ambulatory conditions. Therefore, the lack of change in the spectral components of HR variability that precede the onset of AF episodes may not exclude the significance of the autonomic nervous system as an important trigger of the onset of AF.

### Potential Pathophysiologic Background for the Spontaneous Onset of AF
The normal complexity (ApEn of ≈ 1.0) and fractal characteristics of R-R interval dynamics have been suggested to be markers of healthy cardiovascular regulation. Any deviation from the normal R-R interval dynamics may predispose patients to unfavorable cardiac events. From this dynamic point of view, the reduced R-R interval complexity might thus by itself serve as a trigger of the onset of AF. Although the ApEn

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**TABLE 3. Nonlinear HR Variability Measures and the Amount of Ectopic Beats Before AF Episodes in Nonmedicated Patients (n=11)**

<table>
<thead>
<tr>
<th>Time Period Before AF</th>
<th>120–100 min</th>
<th>100–80 min</th>
<th>80–60 min</th>
<th>60–40 min</th>
<th>40–20 min</th>
<th>20–0 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApEn</td>
<td>1.09±0.26</td>
<td>1.20±0.18</td>
<td>1.17±0.22</td>
<td>1.10±0.25</td>
<td>1.10±0.21</td>
<td>1.02±0.30†</td>
</tr>
<tr>
<td>ApEn (unedited data)</td>
<td>1.05±0.28</td>
<td>1.12±0.23</td>
<td>1.09±0.27</td>
<td>0.99±0.27</td>
<td>0.99±0.27</td>
<td>0.86±0.26*</td>
</tr>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1.29±0.27</td>
<td>1.33±0.20</td>
<td>1.25±0.27</td>
<td>1.26±0.25</td>
<td>1.27±0.23</td>
<td>1.25±0.26‡</td>
</tr>
<tr>
<td>α&lt;sub&gt;3&lt;/sub&gt; (unedited data)</td>
<td>1.03±0.30</td>
<td>1.05±0.36</td>
<td>0.99±0.29</td>
<td>0.97±0.27</td>
<td>1.00±0.32</td>
<td>0.96±0.29‡</td>
</tr>
<tr>
<td>Ectopics, %</td>
<td>1.9±3.6</td>
<td>2.5±5.3</td>
<td>2.5±5.9</td>
<td>3.0±6.0</td>
<td>3.9±6.0</td>
<td>3.3±4.0†</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2. *P<0.001, †P<0.05, ‡P=NS.

**TABLE 4. Nonlinear Measures of HR Variability in Healthy Controls and in Nonmedicated Patients With AF (n=11)**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>AF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF episodes, n</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>ApEn (edited data)</td>
<td>0.99±0.23</td>
<td>1.07±0.29‡</td>
</tr>
<tr>
<td>ApEn (unedited data)</td>
<td>1.02±0.30</td>
<td>0.89±0.27†</td>
</tr>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt; (edited data)</td>
<td>1.34±0.17</td>
<td>1.21±0.26†</td>
</tr>
<tr>
<td>α&lt;sub&gt;3&lt;/sub&gt; (unedited data)</td>
<td>1.27±0.21</td>
<td>0.91±0.28*</td>
</tr>
</tbody>
</table>

*P<0.001, †P<0.05, ‡P=NS as tested with Student’s t-test.
and $\alpha_1$ values were lower before the onset of AF than those from healthy controls, significant overlapping occurred in the individual values. Therefore, altered R-R interval behavior is more likely a marker of a change in cardiovascular autonomic regulation that preconditions the onset of AF in subjects with abnormal electrophysiological properties of the atria rather than being causally related to the onset of AF.

In experiments with artificial and real R-R interval signals, the fixed coupling of premature beats resulted in a reduction of ApEn values, but variable coupling resulted in an increase of ApEn. Thus, a reduction of ApEn before the onset of AF in patients with an increase in premature atrial beats resulted mainly from atrial ectopy with fixed coupling intervals, suggesting an increase of firing from a single atrial focus. Consistent with recent observations of the importance of ectopic firing as a trigger of paroxysmal AF in subjects indicating the coupling intervals.

The physiological determinants of ApEn and $\alpha_1$ have not been well defined. The dynamics of R-R interval variability are the result of a complex interaction between autonomic tone, sensory input, central influence, vasomotor regulation, and target organ responsiveness. Further studies will be needed to establish the mechanisms behind the altered complexity and the fractal characteristics of HR behavior to better understand the physiological correlates of the spontaneous onset of AF.

### Limitations of the Study

Many patients were on medication during the Holter recordings, which may have influenced the measures of HR variability. However, the results remained the same in a subgroup of patients who were not on medication, which suggests that the cardiac medication itself had no major effect on these observations. A relatively small sample of patients was included in this study, and the results should be confirmed in larger patient groups before generalizing these observations. Finally, new nonlinear HR variability measures are rather complex, and their physiological determinants are not well defined. Therefore, further research on the physiological background of these new HR variability indices and on their clinical usefulness in various settings will be needed.

### Conclusions

The number of ectopic beats increases before the onset of paroxysmal episodes of AF in patients with no structural heart disease. Moreover, an alteration of short-term, fractal-like, correlation properties and a reduced complexity of R-R interval data precede the onset of AF episodes. None of the traditional time and frequency domain measures showed any significant changes before AF episodes. These observations confirm the hypothesis that the normal complexity and fractal properties of HR behavior are important for the maintenance of healthy cardiovascular dynamics and that analyzing HR behavior by new methods can provide clinically important information on abnormal cardiovascular regulation that cannot be uncovered by traditional analyses of HR variability.

### Acknowledgments

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### References


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