Prediction of Paroxysmal Atrial Fibrillation Using Nonlinear Analysis of the R-R Interval Dynamics Before the Spontaneous Onset of Atrial Fibrillation

Dong-Gu Shin, MD; Cheol-Seung Yoo, PhD*; Sang-Hoon Yi, PhD*,**; Jun-Ho Bae, MD; Young-Jo Kim, MD; Jong-Sun Park, MD; Geu-Ru Hong, MD

Background  New methods based on nonlinear theory have been developed to give more insight into complex heart rate (HR) dynamics. This study was designed to test the hypothesis that altered HR dynamics, as analyzed with complexity and fractal measures, may precede the spontaneous onset of paroxysmal atrial fibrillation (PAF). Secondly, the difference in the temporal change of these measurements between the different types of atrial fibrillation (AF) was assessed.

Methods and Results  From 105 Holter tapes in which PAF was recorded, 44 PAF (≥5 min) episodes in 33 patients (22 men, 58±12 years), preceded by sinus rhythm for more than 1 h, were selected and submitted to time- and frequency-domain HR variability analyses, along with detrended fluctuation analysis, approximate entropy (ApEn) and sample entropy (SampEn). The 60 min before the onset of AF were divided into 6 10-min periods and studied using repeated measures ANOVA. PAF episodes were divided into 3 subgroups: an increased HF component and decreased L/H ratio (vagal type, n=20); increased L/H ratio and decreased HF component (sympathetic type, n=14); and non-related type (n=10). None of the time- or frequency-domain parameters showed any significant change before AF in any type of AF. The ApEn showed a tendency to decrease before the onset of AF and the change in ApEn was divergent according to the AF type. The ApEn decreased before the onset of AF (1.005±0.046, 60–50 min before AF to 0.894±0.052, 10–0 min before AF; p=0.032). The SampEn also decreased progressively before the start of AF (1.165±0.085, 60–50 min before AF to 0.887±0.077, 10–0 min before AF; p=0.003). The decrease in both the ApEn and SampEn was irrespective of the AF type.

Conclusions  A reduction in the ApEn and SampEn, which reflects the nonlinear complexity of HR variability, is a hallmark of altered HR dynamics preceding the spontaneous onset of AF. (Circ J 2006; 70: 94–99)

Key Words: Autonomic nervous system; Heart rate; Nonlinear complexity; Paroxysmal atrial fibrillation

Atrial fibrillation (AF) is an arrhythmia commonly encountered in clinical practice and a major threat to public health1,2. Paroxysmal AF (PAF) can be classified into vagally-mediated and sympathetically mediated types based on the autonomic profile and the clinical history.3 Analysis of heart rate variability (HRV) preceding the spontaneous onset of AF is a noninvasive method of evaluating autonomic tone and enables documentation of the mechanism.4 Several studies have demonstrated fluctuation in autonomic tone before the onset of AF, but the results are inconsistent.5–9 Recently, nonlinear methods of HRV analysis have been shown to provide information about the dynamics of heart rate (HR) not evident with conventional methods of analysis10–14 and to predict the atrial and/or ventricular arrhythmia risk in a specific disease set.15–18, This study tested the hypothesis that altered R-R interval dynamics, as analyzed with complexity and fractal measurements, may precede the onset of PAF. Second, we assessed the difference in the temporal change of these measures before the spontaneous onset of AF.

Methods

Study Population

From 105 Holter recordings in which 1 or more AF episode(s) was recorded, PAF episodes were selected for analysis if the following criteria were met: (1) documentation of at least 1 episode of PAF (≥5 min), (2) presence of noise-free normal sinus rhythm (SR) for >60 min before AF, and (3) no evidence of sinus node dysfunction or...
Table 2 Changes in R-R Dynamics Before the Spontaneous Onset of Atrial Fibrillation (AF)

<table>
<thead>
<tr>
<th>Time period before AF (min)</th>
<th>60–50</th>
<th>50–40</th>
<th>40–30</th>
<th>30–20</th>
<th>20–10</th>
<th>10–0</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, ms</td>
<td>867±28</td>
<td>861±29</td>
<td>845±28</td>
<td>851±29</td>
<td>859±28</td>
<td>856±29</td>
<td>0.579</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>284±3</td>
<td>263±4</td>
<td>325±5</td>
<td>376±5</td>
<td>345±3</td>
<td>446±6</td>
<td>0.047</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>4.7±1.0</td>
<td>4.7±1.1</td>
<td>5.1±1.1</td>
<td>5.8±1.3</td>
<td>5.5±1.1</td>
<td>8.2±1.5</td>
<td>0.080</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>314±197</td>
<td>208±51</td>
<td>208±37</td>
<td>281±63</td>
<td>280±46</td>
<td>520±147</td>
<td>0.075</td>
</tr>
<tr>
<td>LF/HF</td>
<td>355±4</td>
<td>35±12</td>
<td>35±14</td>
<td>53±34</td>
<td>53±34</td>
<td>51±33</td>
<td>0.185</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>153±35</td>
<td>105±22</td>
<td>201±64</td>
<td>183±45</td>
<td>167±36</td>
<td>249±56</td>
<td>0.040</td>
</tr>
<tr>
<td>nHF, %</td>
<td>362±3</td>
<td>36±5</td>
<td>32±3</td>
<td>34±3</td>
<td>36±3</td>
<td>39±3</td>
<td>0.354</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.49±0.37</td>
<td>2.38±0.32</td>
<td>1.95±0.24</td>
<td>2.19±0.33</td>
<td>1.99±0.29</td>
<td>1.59±0.21</td>
<td>0.028</td>
</tr>
<tr>
<td>ApEn, unedited</td>
<td>0.76±0.062</td>
<td>0.74±0.058</td>
<td>0.68±0.054</td>
<td>0.72±0.059</td>
<td>0.72±0.057</td>
<td>0.68±0.052</td>
<td>0.228</td>
</tr>
<tr>
<td>ApEn, edited</td>
<td>0.98±0.036</td>
<td>0.99±0.033</td>
<td>1.01±0.030</td>
<td>0.98±0.033</td>
<td>1.01±0.032</td>
<td>1.02±0.040</td>
<td>0.374</td>
</tr>
<tr>
<td>SampEn, unedited</td>
<td>0.92±0.036</td>
<td>0.91±0.035</td>
<td>0.94±0.033</td>
<td>0.86±0.031</td>
<td>0.94±0.033</td>
<td>0.95±0.042</td>
<td>0.546</td>
</tr>
<tr>
<td>SampEn, edited</td>
<td>1.00±0.046</td>
<td>1.09±0.040</td>
<td>1.04±0.034</td>
<td>1.00±0.044</td>
<td>1.00±0.044</td>
<td>0.89±0.052</td>
<td>0.032</td>
</tr>
<tr>
<td>ApEn, unedited</td>
<td>0.91±0.048</td>
<td>0.94±0.046</td>
<td>0.84±0.043</td>
<td>0.86±0.043</td>
<td>0.86±0.043</td>
<td>0.76±0.044</td>
<td>0.106</td>
</tr>
<tr>
<td>SampEn, edited</td>
<td>1.16±0.085</td>
<td>1.23±0.070</td>
<td>1.07±0.066</td>
<td>1.09±0.071</td>
<td>1.06±0.080</td>
<td>0.88±0.070</td>
<td>0.003</td>
</tr>
<tr>
<td>Ectopic, %</td>
<td>4.7±1.6</td>
<td>5.7±1.7</td>
<td>6.6±1.8</td>
<td>8.3±2.1</td>
<td>6.9±1.9</td>
<td>9.2±2.1</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Values are mean±SE.
RMSSD, root mean square of the differences of successive normal sinus R-R intervals; pNN50, percentage value of consecutive R-R intervals with absolute differences of more than 50 ms; LF, low frequency; nHF, normalized HF power; ApEn, approximate entropy; SampEn, sample entropy.
*p value for linear trend tested with repeated measure of ANOVA.

Conduction disturbances. None of the patients was taking antiarrhythmic medications, such as amiodarone or β-blockers, at the time of the Holter recordings. The presence of structural heart disease was confirmed by the history, physical examination, ECG, echocardiography and exercise stress test. Forty-four episodes of PAF in 33 patients (22 men, 58±2 years; 1.3 episodes per patient) without structural heart disease were suitable for analysis (Table 1).

Holter ECG Recordings

The 24-h ECG recordings were obtained with a 3-channel digital recorder (SeerMC®, Marquette Electronics Inc) with 125-Hz sampling and were processed by a Marquette MARS 8000 system using MARS software version 4.0 (Milwaukee, WI, USA). The mean recording time of the Holter recordings was 22.9±1.3 h. Each beat was classified and labeled with respect to its site of origin using template-matching techniques. An experienced observer manually reviewed and corrected all tracings if necessary. The Holter ECG data were then imported into a PC for HRV analysis. All questionable portions were compared with raw Holter ECGs.

HRV Analysis

The 60-min period of normal SR preceding the onset of sustained AF, was divided into 6 10-min periods. Only segments with >85% qualified sinus beats were included. These 44 episodes of PAF were divided into 3 subgroups: (1) onset of PAF accompanied by an increased high frequency (HF) component (HF power of 10 min period just before the start of AF is above the mean level of whole observation period) and decreased low frequency (LF)/HF ratio was designated as the vagal type (n=20); (2) the sympathetic type (n=14) had an increased LF/HF ratio and decreased HF component; (3) other episodes that did not belong to either the sympathetic or vagal type were designated as the non-related type (n=10).

Time- and Frequency-Domain HRV Analysis

We calculated the mean, standard deviation (SDNN) and root mean square of the differences (RMSSD) of successive normal sinus R-R intervals. The pNN50, which is the percentage value of consecutive R-R intervals with absolute differences of more than 50 ms, was also calculated. In the frequency domain, a spectral analysis was performed by an autoregressive (AR) algorithm. A modified covariance method was used to solve the AR model. For the AR model-based spectrum, the powers were calculated by integrating the spectrum over each frequency band: the powers of a very LF (0–0.04 Hz), LF (0.04–0.15 Hz), and HF (0.15–0.4 Hz) bands in absolute and relative values, the normalized power of the LF and HF bands, and the LF to HF ratio.

Detrended Fluctuation Analysis (DFA)
The DFA method was used to quantify the fractal-like scaling properties of the R-R interval data. This technique is a modification of the root-mean-square analysis of random walks applied to non-stationary data. In this method, a fractal-like signal resulted in a scaling exponent value of 1. White Gaussian noise (totally random signals) resulted in a value of 0.5, and a Brownian noise signal with a spectrum of rapidly decreasing power in the higher frequencies resulted in an exponent value of 1.51.10–20 In this study, the heart period correlations were defined separately for short-term (<11 beats) and intermediate -term (>11 beats) fluctuations in the R-R interval data.

Approximate Entropy (ApEn) and Sample Entropy (SampEn)

ApEn is a measure quantifying the regularity of time series. It measures the logarithmic likelihood of which runs of patterns that are close to each other will remain close in the next incremental comparisons. A greater likelihood of remaining close (ie, high regularity) produces smaller ApEn values, and conversely random data produces higher values. The ApEn algorithm has been published else-
where. Two input variables, m and γ must be fixed in order to calculate ApEn. In our study, m=2 and γ=20% of the SDNN of the data sets were chosen as suitable values.

The recently proposed SampEn that properly deals with a bias induced from a finite data length and is self-matched in calculating the ApEn, was also used to quantify the complexity of short HR time series A lower value for ApEn or SampEn reflects a higher degree of regularity and predictability.
Nonlinear Dynamics in PAF

Statistical Analysis
Statistical analyses were performed using SPSS for Windows. Comparisons of data obtained at different time intervals were performed using repeated measures ANOVA. A 2-tailed Student’s t-test was used to compare the results of the HRV parameters between groups. Categorical data were compared between groups with Fisher’s exact test. Regression analysis was performed to assess relationships between time and frequency domain and nonlinear HRV measurements. All values are expressed as mean±SE. A significant difference was considered to exist for p<0.05.

Results
Change in the Conventional Time- or Frequency-Domain HRV Parameters
Table 2 presents the HRV measurements and number of ectopic beats during the 6 10-min time periods in all PAF episodes. The only time- or frequency-domain parameters that showed significant changes before the onset of AF were the RMSSD, HF and LF/HF ratio. The RMSSD increased progressively before the start of AF (from 28±3 ms, 60–50 min before AF, to 44±6 ms, 10–0 min before AF; p=0.017). The HF power increased from 153±35 ms², 60–50 min before AF, to 249±56 ms², 10–0 min before AF (p=0.040). The LF/HF ratio decreased progressively before the onset of AF.

Changes in Nonlinear Measures and the Effect of Editing Ectopic Beats
The number of ectopic beats had a tendency to increase before the onset of AF (4.7±1.6%, 60–50 min before AF to 9.2±2.1%, 10–0 min before AF; p=0.067). The ApEn analyzed from the edited data decreased progressively before the onset of AF (1.005±0.046, 60–50 min before AF to 0.894±0.052, 10–0 min before AF; p=0.032, Table 2). When the ApEn was analyzed from the real R-R interval data without any editing of the ectopic beats, an even more prominent reduction was observed in the complexity of the R-R interval dynamics before the onset of AF (Table 2, Fig 1). The SampEn also decreased progressively with a better probability value before the start of AF (1.165±0.085, 60–50 min before AF to 0.887±0.077, 10–0 min before AF; p=0.003). The result in the SampEn before the start of AF was not affected whether excluding the ectopic beats or not. The q1 showed a tendency to decrease before the onset of AF when all ectopic beats were abolished. When analyzed from the data that included ectopic beats, q1 did not change significantly before the onset of AF. The q1 had no significant change before the onset of AF (Table 2).

Comparison of Conventional HRV Parameters and the Nonlinear Measures of HR Dynamics According to AF Type
When the same analyses were performed for the 2 subgroups of AF, which had different autonomic profiles, a significant decrease before the onset of AF was seen in the ApEn and SampEn values calculated from both edited and unedited data. The decrease in both the ApEn and SampEn values was irrespective of the AF type (Fig 2). However, the q1 from both the edited and unedited data showed a divergent change that was not statistically significant (Fig 2). The q1 increased before the onset of AF in the sympathetic type of AF, in contrast to the vagal type in which the q1 decreased before AF. None of the time- or frequency-domain measurements showed any significant change before AF in either type of AF.

Correlation Between Conventional HRV Parameters, Number of Ectopic Beats, and Fractal and Complexity Measures
Significant negative correlations among RMSSD, pNN50 and fractal and complexity measures were present (Table 3). It is notable that q1 correlated positively with nHF and LF/HF ratio and negatively with nHF in contrast to the ApEn and SampEn (Table 3). There was also a significant negative correlation between the number of ectopic beats and the fractal and complexity measures. The Pearson’s correlation coefficient between the number of ectopic beats and q1 was –0.383 (p<0.0001) with editing, and –0.465 (p<0.0001) without editing of ectopic beats. A significant correlation between the number of ectopic beats and the ApEn for both the edited and unedited data was present (correlation coefficients =–0.418, p<0.0001; –0.452, p<0.0001, respectively). The SampEn also showed a similar result to that of the ApEn (correlation coefficients =–0.424, p<0.0001; –0.434, p<0.0001, respectively).

Discussion
We have demonstrated that altered R-R interval dynamics, revealed by a method of describing the complexity and predictability of HR behavior, precede the spontaneous onset of PAF in patients who have no evidence of structural heart disease. The main finding of this study is that ApEn and SampEn, the measures quantifying the complexity of HR dynamics, might be useful markers for predicting the onset of AF, because they show a consistent linear reduc-

Table 3  Correlation Matrix Between Analysis Parameters (n=264)

<table>
<thead>
<tr>
<th></th>
<th>ApEn</th>
<th>SampEn</th>
</tr>
</thead>
<tbody>
<tr>
<td>R*</td>
<td>p value</td>
<td>R*</td>
</tr>
<tr>
<td>Mean, ms</td>
<td>0.092</td>
<td>0.135</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>–0.505</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>–0.605</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nLF, %</td>
<td>0.589</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nHF, %</td>
<td>–0.514</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.694</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ectopics, %</td>
<td>–0.383</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>–0.434</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

See Table 2 for abbreviations.
*Pearson’s correlation coefficients.
tion irrespective of AF type, whereas there was a divergent temporal shift in $\theta_0$ and time- and frequency-domain HRV parameters before the onset of AF.

**Time- and Frequency-Domain Analysis of HRV Before AF**

None of the conventional HRV measurements, except for the RMSSD, HF and LF/HF ratio, exhibited a significant change before the onset of AF in this study. In contrast to previous studies in which no significant changes in the conventional HRV parameters were observed, in the present study the RMSSD and HF component increased and the LF/HF decreased before the start of AF. We speculate that this difference is related to the proportion of vagally or sympathetically mediated types of PAF episodes in the study population, which may also explain a subtle difference between the studies on the autonomic mechanisms of AF onset. Because almost 50% of all PAF episodes included in the present study were the vagal type, we consider that our result is as expected. When analyzed separately after dividing the PAF episodes into vagal and sympathetic types, a temporal shift in the autonomic tone before AF was opposite in direction depending on the AF type. In addition, spectral analysis techniques have several inherent limitations related to non-stationary data during uncontrolled conditions and an inevitable information leakage resulting from the editing of ectopic beats. Thus, these are some of the reasons why spectral analysis may not be able to detect subtle abnormalities in cardiac autonomic regulation that occur in ambulatory conditions.

**Superiority of the Nonlinear Complexity Measures for the Prediction of AF Onset**

The DFA, based on a modified root mean square analysis of random walk, has been widely adopted in the physical and biological sciences. Measurement of the short-term fractal-like correlation properties of HR dynamics, $\theta_0$, has been shown to be a useful prognostic indicator of adverse events in cardiac patients and a powerful descriptor of a healthy aging process. A reduced $\theta_0$ is the most powerful HRV index for predicting the spontaneous onset of ventricular fibrillation; however, the role of this short-term scaling exponent in predicting the onset of AF is unclear. In the present study, the reduction in $\theta_0$ before the start of AF is that HR become more orderly before AF; that is, there is a loss of normal ‘healthy’ complexity. The clinical value of a measure of ‘complexity’ is that complexity appears to be lost in the presence of illness. The complexity measurements have already provided important information in many cardiac conditions. HR becomes more orderly with age and in men exhibiting decreased ApEn. The meaning of the progressive reduction of ApEn before the start of AF is that HR become more orderly before AF; that is, there is a loss of normal ‘healthy’ complexity and development of an environment that is vulnerable to the occurrence of AF. The ApEn has demonstrated the capacity to predict atrial arrhythmias, including spontaneous and postoperative AF after cardiac surgery. The recently proposed SampEn, which properly deals with the bias induced from a finite data length and is self-matched when calculating the ApEn, was also analyzed to quantify the complexity of short HR time series in our study. The decrease in the SampEn before AF was similar to that of the ApEn and it also was irrespective of the AF type. This supports the superior role of ApEn data in predicting AF. The ApEn is a measure of the underlying ‘complexity’ of the system producing the dynamics. The complexity of a measure of complexity is that complexity appears to be lost in the presence of illness. The complexity measurements have already provided important information in many cardiac conditions. HR becomes more orderly with age and in men exhibiting decreased ApEn. The meaning of the progressive reduction of ApEn before the start of AF is that HR become more orderly before AF; that is, there is a loss of normal ‘healthy’ complexity and development of an environment that is vulnerable to the occurrence of AF. The ApEn and SampEn had a significant negative correlation with the number of ectopic beats, similar to the $\theta_0$. There was a negative correlation with RMSSD and with pNN50, but not with LF or HF power, which suggests that autonomic modulation is not a major determinant of the values of ApEn or SampEn. We have shown that the decrease in SDNN, RMSSD, and HF power, and in our study we also observed a significant negative correlation between $\theta_0$ and RMSSD, and HF power, which suggests that autonomic tone has an important influence on the values of the short-term scaling exponent $\theta_0$. Both the fractal and complexity measures of HRV can be influenced by changes in the breathing pattern. As shown in this study, these measures are also influenced by the number of ectopic beats. Thus, these measures would be a composite marker connoting the complexity interactions of neurohormonal regulation of HRV. However, physiological background data of these newer nonlinear measures of HRV, including $\theta_0$, are still limited and inconsistent so careful interpretation is needed. The $\theta_0$ quantifies the correlation properties of the short-term HR dynamics and a reduction implies a change in the short-term HR dynamics to a more random state before the onset of AF.

Another approach to the nonlinear analysis of HR dynamics is quantification of the complexity from the point of view of information theory. The entropy measurement for quantifying the regularity of a time series is the ApEn, which measures the logarithmic likelihood of which runs of patterns that are close to each other will remain close in the next incremental comparison. A greater likelihood of remaining close (ie, high regularity) produces smaller ApEn values, and conversely random data produces higher values. It has been previously described that ApEn values are close to 1.0 in healthy humans. A stepwise, linear reduction in the ApEn values, when analyzed in 6-10 min time periods before the onset of AF, was the most uniform and consistent finding in the present study. It is noteworthy that the decrease in the ApEn before AF was irrespective of the AF type and was not affected by editing of ectopic beats. The recently proposed SampEn, which properly deals with the bias induced from a finite data length and is self-matched when calculating the ApEn, was also analyzed to quantify the complexity of short HR time series in our study. The decrease in the SampEn before AF was similar to that of the ApEn and it also was irrespective of the AF type. This supports the superior role of ApEn data in predicting AF. The ApEn is a measure of the underlying ‘complexity’ of the system producing the dynamics. The clinical value of a measure of complexity is that complexity appears to be lost in the presence of illness. The complexity measurements have already provided important information in many cardiac conditions. HR becomes more orderly with age and in men exhibiting decreased ApEn. The meaning of the progressive reduction of ApEn before the start of AF is that HR become more orderly before AF; that is, there is a loss of normal ‘healthy’ complexity and development of an environment that is vulnerable to the occurrence of AF. The ApEn has demonstrated the capacity to predict atrial arrhythmias, including spontaneous and postoperative AF after cardiac surgery. The results of those studies are consistent with our present observations. A reduced complexity of the R-R interval dynamics is a common denominator preceding the onset of AF, which is independent of the clinical condition and cause of the underlying heart disease. The ApEn and SampEn had a significant negative correlation with the number of ectopic beats, similar to the $\theta_0$. There was a negative correlation with RMSSD and with pNN50, but not with LF or HF power, which suggests that autonomic modulation is not a major determinant of the values of ApEn or SampEn. We have shown that the decrease in...
ApEn is consistent whether HR is slowed down (vagal type) or accelerated (sympathetic type) before AF. Thus, we can conclude that ApEn and/or SampEn are more useful and robust than other parameters tested in this study for monitoring HR dynamics for the prediction of AF.

Study Limitations

A relatively small number of patients was included in this study, and the results should be confirmed in a larger group before generalizing these observations. The observation period before AF was just 1 h, which was divided into 6 10-min time spans. Shorter time periods compared with other studies might affect the results. However, short-term 10-min ECG recordings were sufficient for obtaining representative recordings despite the variability in the magnitude of nonlinear parameters between the long- and short-term R-R interval data.

Despite recent achievements in the treatment of AF over the past decade, it still remains as an important cause of morbidity and mortality. The use of nonlinear parameters, such as ApEn, will give new insights into the pathophysiology of AF and its management. However, these new nonlinear measures are rather complex, and their physiological determinants are not well defined, so careful interpretation of the meaning of the change in the setting of AF onset is needed.

Conclusion

An alteration in the short-term fractal correlation properties and reduced complexity of the R-R interval data precedes the onset of AF episodes. A progressive linear reduction in the ApEn and SampEn, which reflects the decreased complexity of HRV, is a hallmark of altered HR dynamics preceding the spontaneous onset of AF. These nonlinear measures might be useful for monitoring and predicting the occurrence of AF.

References