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Decrease in the heart rate complexity prior to the onset of atrial fibrillation

Volkan Tuzcu[1]*, Selman Nas[1], Tülay Börklü[2], and Ahmet Ugur[3]

[1] *Department of Pediatrics, Division of Cardiology, Arkansas Children's Hospital, University of Arkansas for Medical Sciences, 800 Marshall Street, Slot 512-3, Little Rock, AR 72202, USA;* [2] *Faculty of Aeronautics and Astronautics, Istanbul Technical University, Maslak, Istanbul 34469, Turkey; and* [3] *Department of Computer Science, Central Michigan University, Mount Pleasant, MI 48859, USA*

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Aims To assess heart rate complexity changes prior to the onset of atrial fibrillation (AF) using sample entropy. It has been proposed that the autonomic nervous system might have a role in the initiation of AF.

Methods and results The study included 25 patients with lone AF. Each record set contained two 30 min records from 25 subjects. Each patient had 30 min records containing the ECG immediately preceding an episode of AF (pre-AF) and 30 min of ECG during a period distant from any episode of AF (AFd). Sample entropy was used for complexity analysis. The sample entropy of R–R intervals was significantly reduced in the pre-AF period compared with the AFd period (0.45 ± 0.25 vs. 0.78 ± 0.46, $P = 0.003$). The pre-AF periods were divided into three successive 10 min segments. There was a significant decreasing trend in entropy towards the onset of AF with linear mixed models ($P = 0.002$).

Conclusions The heart rate complexity is reduced with a significant decreasing trend as assessed by R–R interval entropy prior to the onset of AF. There is a need for well-defined studies with larger patient groups in order to assess the entropy changes further and to look for possible changes, which might predict impending AF episodes.

Introduction

The mechanisms leading to initiation of atrial fibrillation (AF) have been under extensive investigation within the last decade. It has been proposed that the autonomic nervous system might have a role in the initiation of AF. Increased vagal tone can predispose to the development of AF.[1]

Non-linear analysis methods such as entropy and fractal analysis can be valuable in the assessment of various physiological time series signals.[2–4] Application of entropy and fractal analysis of the heart rate data have shown promising results in the assessment of cardiac risks in various conditions.[3,4] Different entropy values can be considered as 'hidden information' contained in physiological time series, indicating the underlying disease mechanism.

A previous study assessed the changes in the non-linear dynamics and concluded that 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.[5] The authors used an approximate entropy method for this purpose. Another study suggested that altered complexity of R–R interval dynamics precedes the AF episodes of patients after coronary artery bypass graft surgery.[6]

The aim of our study was to assess the possible changes in the heart rate complexity prior to the onset of the AF using sample entropy (SampEn). Because of the chaotic nature of the data, we also sought the potential fractal pattern alterations of the R–R intervals prior to the AF episodes. The hypothesis is that changes in cardiac control prior to the onset of AF may occur on all time scales and thus could lead to systematic changes in the scaling properties of the heartbeat dynamics. Elucidating the nature of these changes could lead to a better understanding of the neuro-autonomic feedback mechanisms of cardiac regulation.

Methods

All patients with paroxysmal lone AF from PhysioBank database were included in our study.[7] PhysioBank is a large and growing archive of well-characterized digital recordings of physiological signals and related data for use by the biomedical research community. It is

* Corresponding author. Tel: +1 501 364 1479; fax: +1 501 364 3667.
E-mail address: tuzcuvolkan@uams.edu

available to all researchers through the internet. Holter recordings were available for 25 patients with paroxysmal AF. Each record set contained two 30 min records from 25 subjects. The files contained the digitized ECGs (16 bits per sample, least significant byte first in each pair, 128 samples per signal per second, samples from each channel alternating, nominally 200 A/D units per millivolt). Each patient had 30 min records containing the ECG immediately preceding an episode of AF (pre-AF) and 30 min of ECG during a period distant from any episode of AF (AFd; there was no AF during the 45 min period before the beginning or after the end of the 30 min record). This data set is called unedited data. The edited data are obtained by filtering the unedited data. Simply, the premature atrial complexes (any data that are less or more than three times SD of the mean) were removed.

Non-linear analysis

The Brock, Dechert, and Scheinkman (BDS) test was applied to investigate the potential presence of non-linearity in the data.[8] The description of the BDS test is given in the Appendix. The BDS test was used to determine whether the data were random or not. In the BDS test statistics, the rejection of the null hypothesis (the data being independent and identically distributed) implies that the data were not random, which, in turn, implied the presence of non-linear dependency. However, further tests are needed to distinguish between non-linear stochastic and non-linear deterministic processes.

Approximate entropy (ApEn) has been proposed as a measure of regularity used in clinical studies.[2] A similar, but less biased measure is the sample entropy (SampEn).[3] The main difference is that SampEn simply excludes self-matches in the definition of ApEn and does not employ a templatewise strategy for calculating probabilities.[9] Larger SampEn values indicate greater independence, less predictability, hence greater complexity in the data. This, in turn, may imply that decreased complexity or greater regularity in the time series is associated with disease. A short description of the method is given in the appendix. In SampEn, embedding dimension, m, is usually chosen between 2 and 10. The actual value of the embedding dimension depends on the structure of the data. The tolerance distance, r, is usually chosen between 0.10 and 0.50 SD. In order to have SampEn values to be normally distributed, m should be small enough and r should be large enough to guarantee a sufficient number of matches. In this study, the embedding dimension was chosen as $m = 3$ and tolerance distance $r = 0.20$ SD on the basis of the suggestion of Lake *et al*.[9] SampEn analysis was performed using Matlab 6.5.1 software.

Because of the possibility of the existence of identical patterns in the data, the fractal organization pattern of R–R intervals was also assessed. Fractals provide insight into complex anatomical branching structures that lack a characteristic length scale and certain physiological processes such as heart rate regulation that lack a single time scale. Loss of normal fractal complexity of interbeat interval dynamics has been shown in various clinical syndromes.[10] As a fractal analysis method, detrended fluctuation analysis (DFA) has been used to quantify the fractal-like correlation properties of the R–R interval data.[4] This method is a modified root mean square analysis of a random walk. The root mean square fluctuations of the integrated and detrended data are measured within the observation windows of various sizes and then plotted against the size of the window on a log–log scale. If a fitted line represents this data set well, then there is the identity; slope of this line is the scaling exponent. Details of this method have been previously described.[11] A freeshare code from Physionet is used in order to compute the scaling exponent.

Statistical analysis

Data are expressed as mean values $\pm$ SD. One-way ANOVA was used to assess the statistical significances of differences of continuous variables. Linear mixed models were used to evaluate for possible changes in entropy trend over time. First-order autoregressive structure was selected as the repeated covariance type for assessing the trend in repeated measures of entropy prior to the onset of AF. Statistical analysis was done using SPSS for Windows (13.0). A P-value < 0.05 was considered to be statistically significant.

Results

The BDS test was applied to both edited and unedited data sets for different values of the window length $m = \{2, 3, \ldots, 10\}$ and the filter level $r = \{0.25, 0.50, 0.75, 1.0\}$, where the tolerance distance $\varepsilon = r * \text{SD}$. In all cases, the test rejected the null hypothesis, which indicated that the data were not random.

The SampEn of R–R intervals was found to be significantly reduced in the pre-AF period compared with the AFd period in the unedited data set (0.45 ± 0.25 vs. 0.78 ± 0.46, $P = 0.003$) (*Figure 1*). Edited data, however, showed a less pronounced difference. There was no significant difference between the pre-AF period and the AFd period in the edited data set (0.85 ± 0.47 vs. 1.1 ± 0.51, $P = 0.07$); however, there was still a significant difference. The embedding dimension m is set to 4 for analysis (0.77 ± 0.41 vs. 1.04 ± 0.48, $P < 0.05$) (*Figure 2*).

We divided the pre-AF periods into three successive 10 min segments and analysed with SampEn in order to show the presence of a possible trend. There was a significant decreasing trend towards the onset of AF in the unedited data with the linear mixed models ($P = 0.002$) (*Figure 3*). Similar decreasing trend in entropy was noted with the analysis of edited data ($P = 0.016$) (*Figure 4*).

DFA was performed to find the scaling exponents in the R–R interval data. The results that were obtained by DFA did not reveal any significant difference between the scaling exponents of the pre-AF period and the AFd period of the unedited data (0.67 ± 0.17 vs. 0.73 ± 0.13, $P = 0.15$). A similar result was obtained with the edited data: (0.8 ± 0.2 vs. 0.88 ± 0.16, $P = 0.17$).

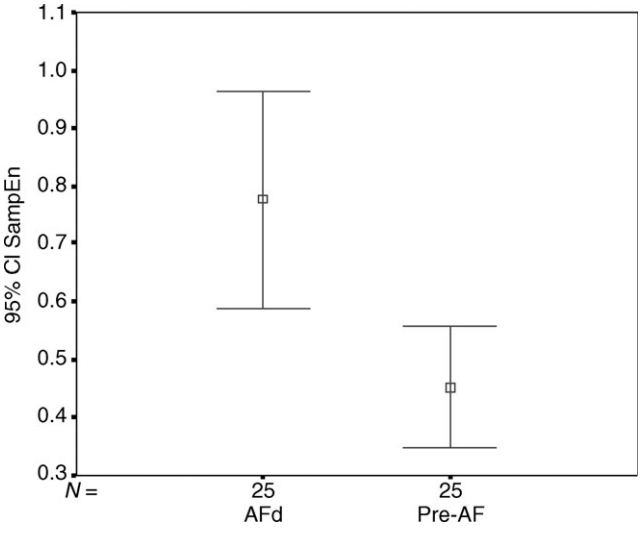

Figure 1 Error bar plots of SampEn values revealing 95% CI of AFd and pre-AF (unedited data, $P = 0.003$).

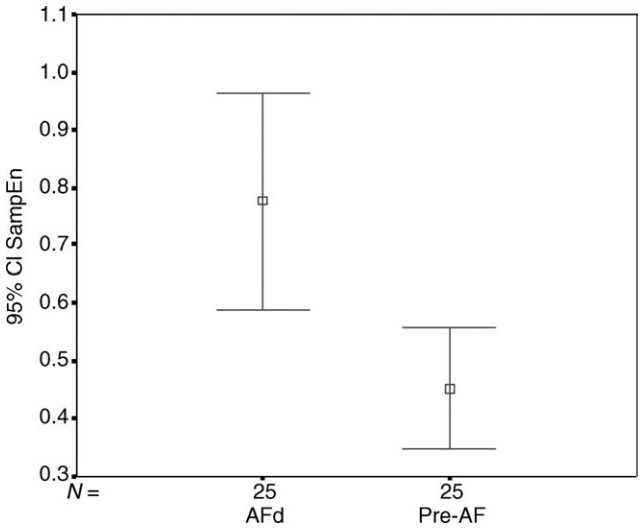

Figure 2 Error bar plots of SampEn values revealing 95% CI of AFd and pre-AF (edited data, $m = 4$, $P < 0.05$).

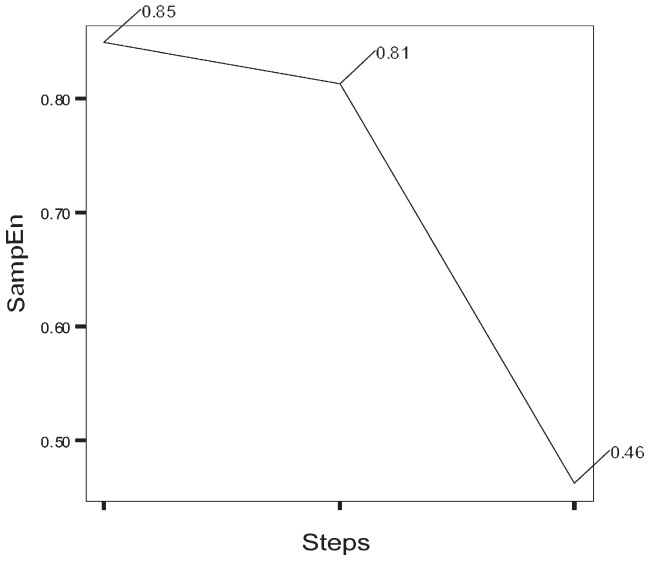

Figure 3 Mean SampEn values of the unedited R–R interval data prior to the AF are represented on the *Y*-axis. 1, 2, and 3 on *X*-axis represent 10 min intervals prior to the AF onset (30, 20, and 10 min before the onset of AF successively) ($P = 0.002$).

Discussion

This study supports the existence of a change in heart rate complexity as assessed by SampEn prior to the onset of AF. Decreased heart rate complexity reflects a change in cardiovascular autonomic regulation that preconditions the onset of AF and is not causally related to the onset of AF. The decrease in SampEn before the onset of AF resulted mainly from atrial ectopy. This is consistent with the observations of the significance of ectopic firing as a trigger for paroxysmal AF in subjects without evidence of other structural cardiac abnormalities.[12] The reduced complexity of R–R interval dynamics before the spontaneous onset of AF was evident even after the removal of ectopic beats. However, the decrease in entropy was less pronounced. Therefore,

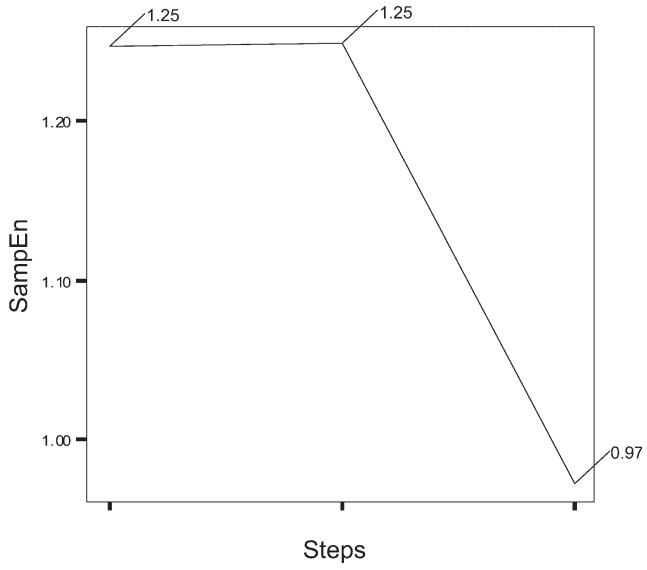

Figure 4 Mean SampEn values of the edited R–R interval data prior to the AF are represented on the *Y*-axis. 1, 2, and 3 on *X*-axis represent 10 min intervals prior to the AF onset (30, 20, and 10 min before the onset of AF successively) ($P = 0.016$).

altered autonomic regulation of sinus node behaviour seems to play a role in the initiation of the spontaneous onset of AF besides the influence of atrial ectopy.

The complexity analysis was found to be very dependent on the premature ectopic atrial beats unlike the study reported by Vikman *et al*.[5] When the data were edited to remove the premature ectopic atrial beats, the heart rate complexity effect was blunted, and in fact, only with a higher value of *m* was a significant difference demonstrated between the two groups.

One of the important differences in the study by Vikman *et al*. and the current one was the fact that we used SampEn rather than ApEn. SampEn was developed to overcome certain limitations of the ApEn method. As indicated earlier, ApEn lacks relative consistency. That is, if ApEn of one data set is higher than that of another, it should, but does not, remain higher for all conditions tested.[13] This shortcoming is particularly important, because ApEn has been repeatedly recommended as a relative measure for comparing data sets. SampEn does not count self-matches. SampEn is largely independent of record length and displays relative consistency under circumstances where ApEn does not.[3]

The second methodological difference between the study reported by Vikman *et al*. and the current study was in the method of artefact-premature ectopic atrial complex removal. We used 3 SD of the mean R–R intervals to define the included beats. R–R intervals below and above 3 SD were excluded. The initial analysis was performed to try different values of SD (from 1 to 5) for editing purposes. Three SD were the most reasonable cut-off value without compromising the data by the elimination of normal beats. Vikman *et al*. excluded the beats that were 30% different from the successive beats. We opted not to use the same method. By editing the data using a 30% cut-off value, a significant amount of normal beats may be eliminated besides ectopic beats, especially in the presence of sinus

arrhythmia. Despite the fact that filtering was performed to remove premature beats as outlined earlier, complexity analysis was also performed using unedited data in order to include the effect of premature atrial beats on the heart rate complexity. In fact, a more prominent difference in SampEn was found between the pre-AF and AFd periods. Vikman *et al*.[5] also found a less pronounced difference in entropy when they edited their data.

One of the important findings of the current study is the demonstration of a significant decreasing trend in R–R interval entropy over time towards the onset of AF. This finding was supportive of the results of Vikman *et al*., which were obtained with ApEn analysis. The decreasing trend in entropy can have very important implications in the investigation of possible predictor changes in the R–R interval entropy for impending AF episodes. Much larger sample size would be necessary to demonstrate potential predictor changes prior to AF.

The BDS analysis showed presence of non-linearity, hence the possibility of chaos in the data. In some chaotic time series, it is possible to make short-time predictions. However, the BDS test does not tell us the actual degree of dependency. Further tests need to be made to assess the actual degree of dependency.

Similar to many physiological systems, DFA results were indicative of the presence of long-range time correlations in the R–R interval data. However, we were unable to demonstrate fractal pattern differences between the pre-AF and AFd periods. This is likely to reflect the various aspects of the altered autonomic regulation, and hence, a decrease in complexity does not necessarily mean that long-range time correlations will be lost. Prospective, controlled studies will be necessary to delineate the details of the autonomic influences prior to the onset of AF.

Study limitations

A small sample of patients was studied. There is a need for similar studies with larger patient groups. Some of these patients were on medications. Possible effect of these medications on the non-linear analysis methods that were used cannot be excluded. However, as these patients were used as their own controls in the comparison of pre-AF with AFd periods, we do not think that this is a factor that could significantly alter our conclusions. Finally, there is a need for further studies to establish the benefits of these relatively new non-linear analysis methods in clinical medicine.

Conclusions and clinical implications

There is reduced heart rate complexity with a significant decreasing trend prior to the onset of AF. There is a need for well-defined studies with larger patient groups in order to assess the entropy changes further and to look for possible changes that might predict impending AF episodes.

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Appendix

The BDS test

A time series x_t is independent and identically distributed if the two following necessary conditions are satisfied:

(1) The mean and variance of x_t are constant.
(2) The autocovariances $\mathrm{cov}(x_t, x_{t-k})$ are all zero for all $k \neq 0$.

The BDS test is used to test the null hypothesis H_0: x_t is independent and identically distributed. The BDS test statistic $S(m, \varepsilon)$ is derived from the correlation integral $C_m(\varepsilon)$ and defined as $S(m, \varepsilon) = C_m(\varepsilon) - [C_1(\varepsilon)]^m$, where correlation integral $C_m(\varepsilon)$ is defined as

$$C_m(\varepsilon) = \lim_{N\to\infty} \frac{1}{N^2} \{\text{number of pairs } (i, j) \text{ such that } |X_{i,m} - X_{j,m}| < \varepsilon\}.$$

Here, $X_{i,m}$ denote m-dimensional vectors (points in phase space) constructed from a time series using the method of delays, N denotes the number of points, m is called the embedding dimension, ε is called the proximity parameter or tolerance distance, and $|\ldots|$ denotes a norm. For large sample sizes, it is shown that $S(m, \varepsilon)$ is normally distributed with mean 0 and variance q, where q depends on m, ε, and sample size. The correlation integral measures the fraction of pairs that lie within the tolerance distance ε for the particular embedding dimension m.

For a particular ε value, if BDS estimates corresponding to various m values converge to small values (usually in the range of -3 to 3), then the data set is considered to be random (i.e. the null hypothesis is accepted).[8]

Sample entropy

For $r > 0$ and m, a positive integer; form vectors $x_i = [u_i, u_{i+1}, \ldots, u_{i+m-1}]$ with u_is generated by a discrete time process $\{U_i\}$. Define the distance such that the distances among vectors are calculated as the maximum absolute distance between their corresponding scalar elements, $d[x_i, x_j] = \max_{k=1,\ 2,\ \ldots,\ m} |u_{i+k-1} - u_{j+k-1}|$. Then, find for each $i \leq N - m + 1$,

$$C_i^m(r) = \frac{\text{number of } j \leq N - m + 1 \text{ such that } j \neq i \text{ and } d[x_i, x_j] \leq r}{N - m + 1}$$

Here, N is the number of data points and m is the embedding dimension. The $C_i^m(r)$s measure within a tolerance distance r the count of patterns similar to a given pattern of window length m. After normalization, define $\phi_r^m = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} \log C_i^m(r)$. The SampEn value is computed by $\mathrm{SampEn}(m, r, N) = \phi_r^m - \phi_r^{m+1}$. This last result can be rearranged such that

$$\phi_r^{m+1} - \phi_r^m = \text{average of log (conditional probability that } |u_{i+m} - u_{j+m}| \leq r, \text{ given that } |u_{i+k} - u_{j+k}| \leq r \text{ for } k = 0, 1, \ldots, m-1).$$

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