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ORIGINAL ARTICLE

Increased Sample Entropy and High Heart Rate Variability Fluctuation in Persistent Atrial Fibrillation as Compared with Paroxysmal Atrial Fibrillation: A Matched Case-Control Study

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Abstract

The relationship between atrial fibrillation (AF) and distortion of autonomic function is reported in the literature. We aim to evaluate sample entropy (SampEn) and heart rate variability (HRV) in patients with persistent AF and compare them with patients suffering from paroxysmal AF. SampEn and HRV during the presentation of AF were analyzed. In patients with persistent AF, there were significant increases in SampEn and increases in the proportion of normal-to-normal (NN) intervals more than 50 ms, NN intervals higher than 50 ms (pNN50), and a decrease in low-frequency power (LF) compared to patients with paroxysmal AF. The major HRV parameters (increased pNN50 and decreased LF) along with nonlinear data (increased standard deviation of the distances the dots lie from the boundary of identity and decreased detrended fluctuation analysis coefficient) provide pieces of evidence based on a neural mechanism underlying AF. The higher SampEn values correlate to the high fluctuation of HRV in persistent AF patients compared to those with paroxysmal AF. In conclusion, increased SampEn and high fluctuation of HRV may induce AF to become persistent.

Keywords: atrial fibrillation; heart rate variability; sample entropy

Introduction

Atrial fibrillation (AF) is heart dysrhythmia due to irregular rhythm in the atria.[1] Inhomogeneous electrical activity in the atrial chamber is related to the occurrence of irregular rhythm in the atria. Total irregularity and re-entrant waves are essential characteristics.[2] Therefore, a chance for conversion into normal sinus rhythm (NSR) of these multiple re-entries is in reverse proportionate to the severity of re-entrant circuits in the atria.[3,4] Several studies revealed the correlation between the number of re-entrant waves in the atrial chamber and the degree of irregularity pattern in atria using signal processing techniques for surface electrocardiogram (ECG) analysis. By applying the nonlinear method, i.e., sample entropy or SampEn, the pattern of atrial signals could be transformed and characterized.[4] Currently, this novel biosignal mechanism is a predictive value for the nature of paroxysmal AF as well as a factor of its recurrence after treatment with external electrical cardioversion (ECV).[1,3,4]

The autonomic nervous system, which contains the balance between sympathetic and parasympathetic parts, plays an essential role in cardiac rhythm control. The sympathetic system provides subepicardial innervation following the courses of the main coronary arteries. While the parasympathetic system supplies subendocardial innervation

across the atrioventricular groove via the vagus nerve.[5] These connections between the heart and the brain, the so-called brain-heart interactions, affect the occurrence of many types of cardiac arrhythmias.[6] One of the ideal conditions for an insight into the brain-heart interaction is insular lobe damage.[7] The evidence supports the role of the insula in cardiovascular autonomic regulation.[8] A clinical study demonstrated that insular infarction was inducing cerebrogenic arrhythmia leading to sudden cardiac death.[9] This finding reflects that brain injury, particularly insular damage, also affects cardiac autonomic regulation and becomes arrhythmogenesis. Therefore, the brain-heart interaction control should give clinical benefit and may prevent the occurrence of AF.

Heart rate variability (HRV) represents autonomic regulation in the heart. Abnormalities in HRV reflect autonomic control disturbances in many cardiac diseases, including AF.[10] HRV is a promising marker for autonomic disturbance in patients with acute cerebral infarct.[11] The decreased HRV was reported in patients with acute cerebral infarct and chronic AF.[12–14] The lower standard deviation of normal-to-normal (NN) RR intervals (SDNNs) is an essential predictor for poor patient outcomes with cerebral infarct.[15]

Furthermore, our previous study has demonstrated significantly reduced HRV (low-frequency power [LF]) in persistent AF compared with paroxysmal AF, reflecting possible relation between HRV and a degree of cardiac autonomic impairment in both AF types.[16] As mentioned earlier, SampEn, a surrogate marker for degrees of irregularity, becomes a new potential predictor for AF recurrence after ECV, including the behavior of paroxysmal AF. Therefore, we aimed to evaluate SampEn and HRV between paroxysmal AF and persistent AF.

Material and Methods

Patients and ECG recordings

Forty cases including 20 paroxysmal AF patients and 20 persistent AF patients, were recruited from October 2013 to September 2014. The study followed through in agreement with the Declaration of Helsinki (2008) of the World Medical Association. Patient care followed appropriate standards of Human Ethics Committee from Faculty of Medicine, Thammasat University, and Faculty of Medicine Ramathibodi Hospital, Mahidol University (EC approval number: MTU-EC-PH-2-061/55, issued on October 08, 2013), Thailand.

The ECG measurements were collected with a sampling rate of 1000 Hz with lead II and V1 for a 5min long duration. We independently matched paroxysmal AF and persistent AF groups concerning age range (< 45, 45–54, 55–64, 65–74, and >74 years), sex, and current CHA_2DS_2-VASc score (cardiac failure or dysfunction or hypertension for 1 point; age > 75 years for 2 points; diabetes mellitus for 1 point; history of stroke for 2 points; vascular diseases for 1 point; age between 65 and 74 years for 1 point, and female gender for 1 point). We selected the related parameters according to the previous postulated effects on AF, cerebral infarct, and HRV.[17] We collected all ECGs under the same circumstances with subjects in a supine position in a comfortable and quiet room. We also performed the inter-rater ECG interpretation in a blinded method.

Sample size

The sample size for this study was calculated according to the pilot data. Normalized LF power in paroxysmal AF versus persistent AF patients were 29 and 18 normalized units (n.u.), respectively. Since the standard deviation (σ) was 12 n.u., the formula from the test of difference of two independent means (at $\alpha = 0.05$ and $\beta = 0.8$) was applied to estimate sample size (n) as follows:

$$
\begin{aligned}
n &= \frac{2(z_{1-\alpha/2} + z_{1-\beta})^2 \sigma^2}{(\mu_1 - \mu_2)^2} \\
&= \frac{2(1.96 + 0.84)^2 12^2}{(29-18)^2} \\
&= 2(3.05)^2 \\
&\sim 19 \text{ patients/group}
\end{aligned}
$$

ECG analysis

Sample entropy

Several studies demonstrated a relationship between the degree of irregularity and the number of re-entrant waves or circuits roaming throughout

the atrial chamber. Therefore, more circuits mean a higher degree of AF disorganization as well as elevated SampEn values.[18,19] SampEn tests repetition in a time series by assigning a non-negative number to the sequence and corresponding the lower values to lower irregularity in the data.[20] Equation (1), was used to compute the SampEn using the negative logarithm of the probability for the similarity between two sequences (during *m* points and the next point) without self-matching.[20] The study by Alcaraz et al.[21] demonstrates that the best m and r values for estimation of AF organization are m = 2 and r = 0.25.

$$\text{Sample entropy}\left(m,r,N\right) = -\ln\frac{C^{m+1}(r)}{C^{m}(r)} \qquad (1)$$

Where m: embedding dimension, r: tolerance parameter, N: data of length, and c:conditional probability.

Lead V1 in surface ECG from patients with AF provides the best atrial signals for SampEn analysis.[1,22] SampEn is the most favorable method to analyze a time series for comparable periods and allocate a non-negative number to the sequence. The higher SampEn represents a greater degree of irregularity.[1] SampEn is also useful for differentiation between terminating and nonterminating in patients with paroxysmal AF and for the prediction of good outcomes after ECV in patients with persistent AF.[3,23]

ECGs with a tracing rate of 1000 Hz, 5min in length from other digital methods, were evaluated under software programs. We modified the principal structure of the software programs from those originally invented by Alcaraz et al.[1] and Bollmann et al.[24] Subsequently, we also applied SampEn evaluation on the remaining 10s long successive TQ interval of the ECG.

Heart rate variability

A standard method and guidelines for a reading of HRV are determined previously.[25] The time-domain measurement of HRV includes root mean square of consecutive differences between normal-to-normal (NN) intervals (rMSSD), a standard deviation of NN intervals (SDNN), and proportion of consecutive NN intervals higher than 50 ms (pNN50). The SDNN reflects the overall HRV and beat-to-beat variations in RR intervals (rMSSD). While the pNN50 represents parasympathetic or vagal activity.[26] Concerning the frequency domain section of HRV, high-frequency power range (HF) corresponds to the respiratory sinus arrhythmia (RSA) and indicates cardiac parasympathetic tone. In contrast, the low-frequency power range (LF) represents a combination of the parasympathetic and sympathetic systems. Furthermore, the LF/HF ratio represents the sympathovagal balance.[11] The quality of standard short-term (5 min) HRV analysis is as reliable as the long-term (24 h) Holter ECGs.[27,28]. In this study, we also used nonlinear HRV, i.e. Poincaré plot analysis, and detrended fluctuation analysis, for more thorough ECG analyses.

Poincaré plot. As complex mechanisms regulate HRV, it consists of nonlinear properties. RR interval Poincaré plot is a well-known nonlinear assessment that corresponds to a quantitative visual technique.[29] This scheme contains a disperse plot of the current RR interval compared with the preceding RR interval. Dots beneath the boundary at 45° to the normal axis or the so-called boundary of identity represent current RR intervals that are shorter than the preceding RR interval, and dots beyond the boundary of identity represent longer RR intervals than the previous ones.[30] A natural approach to visualize the character of the Poincaré plot is to apply an ellipse to the scheme. This ellipse represents the boundary of identity. The scattering of dots along the vertical axis to the boundary of identity indicates short-term variability, quantified by the standard deviation of the distances the dots lie from the boundary of identity (SD1). SD1 indicates the standard deviation of the consecutive differences of the RR intervals (SDSD) or rMSSD,[31] mostly mediated by the parasympathetic system or vagal activity and related to RSA. The standard deviation of dots beside the boundary of identity (SD2) represents the standard deviation of the RR intervals and is related to long-term variability.[32]

Detrended fluctuation analysis (DFA)

DFA is a technique to identify and measure the relationship of physiologic time series. DFA detects not only irregularity but also nonstationary statistical properties changed with time.[33] We evaluated these signal fluctuations by comparing their nature to various noise types seen in dynamic systems.[34] For example, the sequence of RR intervals, which are entirely random, i.e. no relationship exists in the time series, is classified as white noise.

In contrast, if the RR interval at any given moment is solidly associated with the prior interval, it is the so-called random walk or Brownian noise. The DFA technique measures the detrended fluctuations or F (*n*) of a signal at different time scales *n* (Equations (2, 3)). The parameter α, or the scaling exponent approximated by a linear regression fitting of log F (*n*) versus log *n*, measures the relationship of the signal. If α is equal to 0.5, there is no correlation, and the signal is white noise. If α is equal to 1.5, the signal is a random walk. If α is between 0.5 and 1.5, there are positive correlations.[35]

$$F(n)=\sqrt{\frac{1}{N}\sum_{k=1}^{N}(y(k)-y_n(k))^2} \quad (2)$$

$$y(k)=\sum_{j=1}^{k}(RR_j-\overline{RR}),\quad k=1,2,3,\ldots,N \quad (3)$$

Where, N = data of length, RR = the mean of RR interval, and RRj = value of RR interval at j point

The original time series of RR intervals are incorporated and subsequently divided into boxes of equivalent duration, n. For each duration n, a least-squares line, representing the tendency in that box, is suitable to the data. The degree of the fluctuations, or F (n), is subsequently measured as the root mean square deviation between the incorporated RR interval and its tendency in each box. This calculation is duplicated over all time scales or box sizes. A linear relationship on a log-log graph implies the existence of self-similarity, such that fluctuations in small boxes are correlated with that in larger boxes. α represents the gradient of the line relating log F (n) to log n.[34] The associations are usually divided into short- and long-term fluctuations. The short-term fluctuations are characterized by α_1 or the slope acquired from the log-log graph within range $4 \le n \le 16$, while α_2, which determines long-term fluctuations, is the slope acquired from the range $16 \le n \le 64$.

Regarding short-term HRV analysis, the LabChart® HRV module was used for time and frequency domain methods. The Kubios HRV 2.0® software program was used for nonlinear HRV analysis.

Statistical analysis

Data are presented as mean ± standard error. The student's t-test was used for continuous variables comparison and χ^2 test or Fisher's exact test for categorical variables. Pearson's correlation coefficients compare the bivariate correlation between SampEn and HRV variables. A value of $P < 0.05$ is considered statistically significant when the power is 80%.

Results

Table 1 demonstrates the demographic parameters of both groups. No statistically significant difference between clinical characteristics and demographic data was noted (Table 1).

Table 2 demonstrates HRV findings in the time domain of the patients in both groups. Patients with persistent AF had significantly higher heart rate, SDNN, rMSSD, and pNN50 versus paroxysmal AF (Table 2).

The LF and HF power in n.u. are demonstrated in Figure 2. LF in patients with persistent AF is significantly lower versus paroxysmal AF (17 + 2 and 26 + 4 n.u., respectively). In HF and LF/HF ratio, no significant difference between persistent AF and

Table 1 The baseline characteristics of the patients.[a]

Characteristics	Paroxysmal atrial fibrillation patients (n = 20)	Persistent atrial fibrillation patients (n = 20)	P values
Age, years	69 + 3	69 + 2	NS
Female, n (%)	6 (30)	6 (30)	NS
CHF, n (%)	2 (10)	1 (5)	NS
HT, n (%)	12 (60)	13 (65)	NS
DM, n (%)	4 (20)	4 (20)	NS
Vascular diseases, n (%)	3 (15)	1 (5)	NS
CHA_2DS_2-VASc score	4.0 + 0.4	4.2 + 0.4	NS
Use of anticoagulants, n (%)	16 (80)	15 (75)	NS

[a] Values are mean + standard error or n (%). Differences between groups are presented as P values.
CHF, congestive heart failure; HT, hypertension; DM, diabetes mellitus; NS, not significant.

Table 2 Heart rate variability (measured in the time domain) of the patients.[a]

HRV parameters	Paroxysmal atrial fibrillation patients (n = 20)	Persistent atrial fibrillation patients (n = 20)	P values
Heart rate, bpm	70 + 4	85 + 4	< 0.05
SDNN, ms	57 + 15	167 + 13	< 0.01
rMSSD, ms	78 + 24	236 + 18	< 0.01
pNN50, %	10 + 3	78 + 2	< 0.01

[a]Values are mean + standard error and differences between groups are presented as P values.
SDNN, a standard deviation of all normal-to-normal RR intervals; rMSSD, root mean square of differences of adjacent normal-to-normal RR intervals; pNN50, number of normal-to-normal RR intervals differing by more than 50 ms from adjacent interval divided by the total number of all normal-to-normal RR intervals.

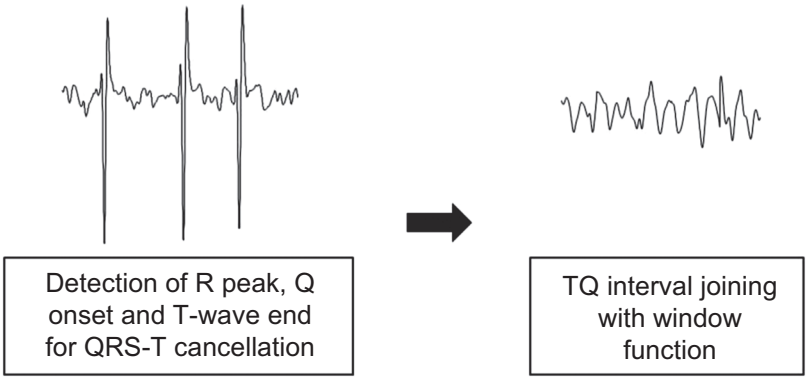

Figure 1 Signal processing diagram to acquire atrial signals without ventricular activities or TQ intervals. A representative TQ interval extracted from ECG by the cancellation of the QRS-T complex was demonstrated.

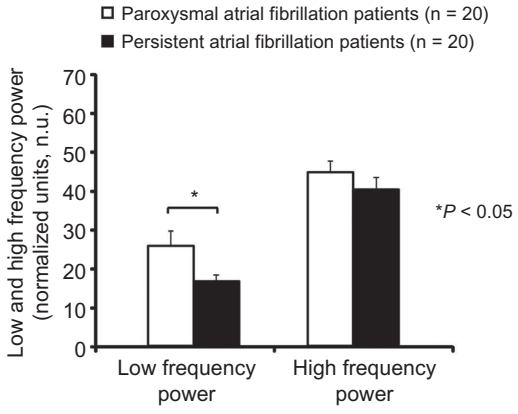

Figure 2 Low-and high-frequency power in normalized units (n.u.) from patients with paroxysmal and persistent AF. P values are shown for the comparison between groups.

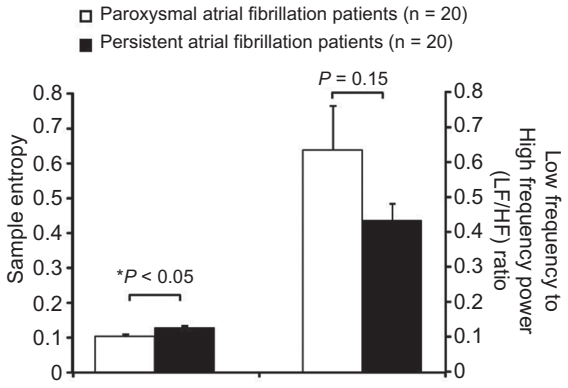

Figure 3 Sample entropy and low- to high-frequency power ratio from patients with paroxysmal and persistent AF. P values are shown for the comparison between groups.

paroxysmal AF groups, i.e., 40 ± 3 vs. 45 ± 3 for HF, and 0.44 ± 0.05 vs. 0.64 ± 0.13 for LF/HF ratio, respectively (Figure 3). Furthermore, from figure 3 SampEn is significantly decreased in patients with paroxysmal AF (0.10 + 0.01) compared with patients with persistent AF (0.13 + 0.01).

The only correlation between SampEn and pNN50 was significant (R = 0.38, $P < 0.05$) after analyzing paroxysmal- and persistent AF groups together. Figure 4 shows that this correlation was more prominent in persistent AF group (R = 0.52, P < 0.05).

Table 3 demonstrates nonlinear HRV analyses of the patients in both groups. SD1 and SD2 for Poincaré plot analysis are higher in the persistent AF group compared with paroxysmal AF. Though

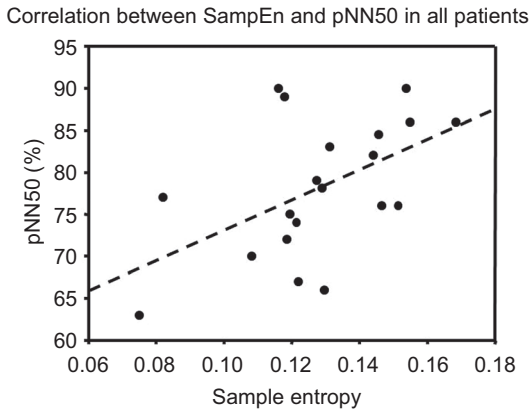

Figure 4 Scatter plot between sample entropy or SampEn and pNN50 in patients with persistent atrial fibrillation. The slope of the regression line (dashed line) indicates positive correlation between SampEn and pNN50 (R = 0.52, P < 0.05). pNN50: number of normal-to-normal RR intervals differing by more than 50 ms from adjacent interval divided by the total number of all normal-to-normal RR intervals.

both DFA variables, α_1 and α_2, are lower in the former group, only α_2 shows a significant difference (Table 3). Figure 5 demonstrates the representatives of the Poincaré plot and DFA oft two pairs of matched patients in each group.

Discussion

In this study, we used a matching method for the best comparisons between paroxysmal and persistent AF groups to eradicate most of the possible confounding factors affecting SampEn and HRV parameters, including age, gender, heart failure, hypertension, and diabetes mellitus. Our study indicates the potential relations between cardiac autonomic modulation determined by an altered HRV and potential marker for the complexity of AF signal, particularly SampEn, in patients with AF. The study demonstrated modulation of primary

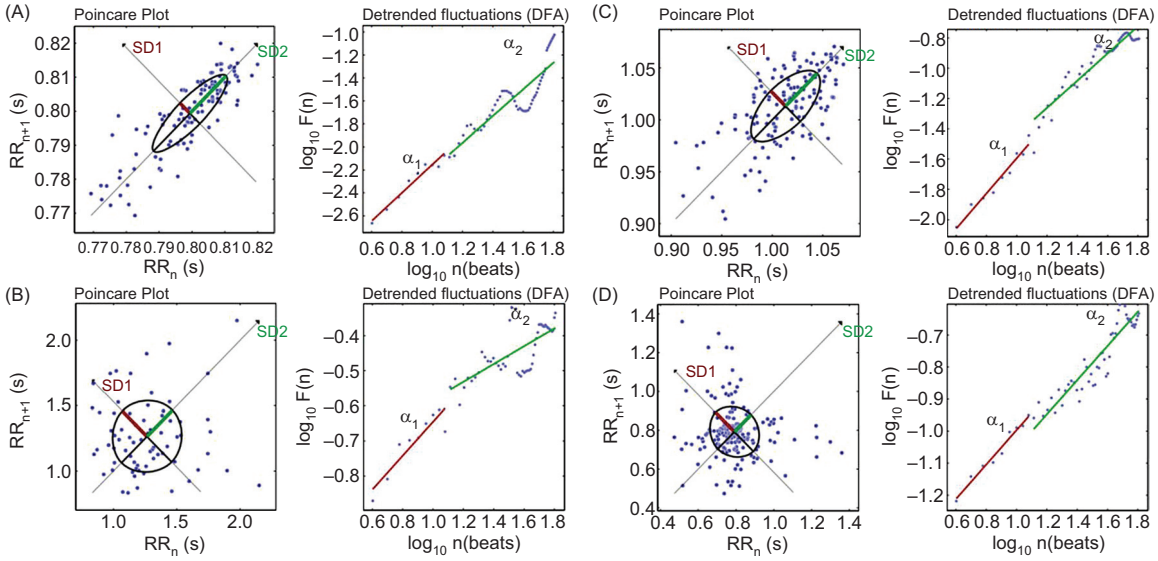

Figure 5 Representative Poincaré plot and detrended fluctuation analysis or DFA of two pairs of matched patients; paroxysmal AF patients (A and C) were matched (according to age, gender, and underlying diseases) with persistent AF patients (B and D, respectively).

Table 3 Nonlinear heart rate variability of the patients.[a]

HRV parameters	Paroxysmal atrial fibrillation patients (n = 20)	Persistent atrial fibrillation patients (n = 20)	P values
SD1, ms	54 + 16	168 + 12	< 0.001
SD2, ms	62 + 16	170 + 13	< 0.001
α_1	0.78 + 0.10	0.60 + 0.02	NS
α_2	0.88 + 0.08	0.46 + 0.04	< 0.001

[a] Values are mean + standard error, and differences between groups are presented as P values.
NS, not significant.

HRV values (both time and frequency domain) reflecting wide fluctuation of HRV, i.e. increased SDNN, rMSSD, pNN50, and decreased LF, in persistent AF patients compared with those in the paroxysmal AF group. Furthermore, we found a close positive correlation between SampEn and pNN50 in all patients, similar to the correlation in the persistent AF group, which could relate to the underlying cardiac autonomic modulation.

The reduction of the atrial refractory period should play an essential role in the re-entry mechanism for the occurrence of AF. The implementation of SampEn in AF supplies a remarkable indicator for unsynchronized atrial activities to evaluate the number of active re-entries and indirectly represent refractory properties within the atrial chamber.[18] Many studies demonstrated that the sympathovagal imbalance might affect re-entry mechanisms in AF.[36,37] According to this assumption, high fluctuation of HRV due to cardiac autonomic modulation in persistent AF could lead to more complicated re-entry and remodeling, or higher SampEn values, compared to paroxysmal AF in this study.

The nonlinear HRV parameters demonstrated a higher degree of beat-to-beat variability or complexity shown by higher SD1 from nonlinear Poincaré plot analysis in persistent AF patients versus those in the paroxysmal AF group. These suggested a relatively high degree of fluctuation in the persistent AF group, consistently with the increased rMSSD and pNN50 in the time domain HRV findings.

The previous study by Vikram et al.[38] demonstrated an alteration of the short-term relationship of RR interval (decreased α_1) preceding the spontaneous occurrence of paroxysmal AF episodes in patients without evidence of structural cardiac disease. This finding was undetectable by conventional time and frequency domain measurements but unveiled by DFA. In our study, both α_1 and α_2 in persistent AF have been shown to decrease compared with paroxysmal AF. The reduced short-term DFA coefficient (α_1) toward 0.5 in both paroxysmal and persistent AF patients from our findings is still consistent with the previous study, which reported a decrease in α_1 (< 1) before the onset of AF episodes.[38]

Nevertheless, the level of altered DFA coefficients was prominent for α_2 compared with α_1 in our study. The possible reason may be associated with the dominant relation between α_2 and aging.[39] The correlation observed from DFA reflects a self organizing mechanism for extremely complex processes (e.g. heart beating) that create fluctuations across a broad range of time scales. Lack of this correlation would narrow the functional responsiveness against any pathological processes as found in aging.[33] In patients with persistent AF, the irregular ventricular response over relatively small time scales (lower α_1 compared to the values in paroxysmal AF patients with NSR) could enhance the degree of decreased long-term DFA coefficient (α_2) to resemble white noise. However, most of our study populations in both groups were elderly subjects with a mean age of 69 years.

Previous studies provided evidence for autonomic alterations related to the short-term DFA coefficient.[39,40] Tulppo et al. [40] reported that cardiac vagal blockade with atropine increased the α_1 value. Moreover, more recently, Castiglioni et al. [39] have confirmed the findings by the study on posture changing from supine to sitting position, which increases autonomic tone fluctuation. They have found that the expected increase in autonomic tone fluctuation is associated with a steeper slope of α_1. Moreover, Bettoni and Zimmermann[41] reported evidence of autonomic tone variations right before the occurrence of paroxysmal AF. Accordingly, our study revealed an increase in α_1 along with changes in other HRV parameters, especially lower rMSSD, pNN50, and SD1, in paroxysmal AF patients, as described previously. Altogether, these indicated lower fluctuation of HRV in paroxysmal AF compared with the persistent AF group and emphasized the role of the autonomic nervous system in the neural mechanism of AF.

Limitations

Only 5 min of collecting time may not be long enough for HRV analysis in the time domain. This critical limitation can lead to the wrong interpretation of HRV. However, long-duration monitoring for HRV with our machine is not possible for ambulatory patients. This disadvantage of the HRV machine is a critical limitation for its use in clinical practice.[42] We tried to analyze both the time and frequency domain to intensify the reliability of HRV interpretation.

Conclusion

In summary, atrial electrical complexity with increased SampEn and cardiac autonomic

modulation with high fluctuation of HRV may induce AF to become persistent. Further studies are needed to confirm this hypothesis.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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