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ORIGINAL ARTICLES

Atrial electrophysiological property analysis by sample entropy and atrial fibrillatory rate with cardiac autonomic derangements in acute ischemic stroke with atrial fibrillation

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Abstract

Background & Objective: Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with risk of ischemic stroke. Atrial electrophysiological properties are influenced by alteration of cardiac autonomic tone. Cardiac autonomic derangement was reported in acute ischemic stroke patients. Atrial activity analysis with sample entropy (SampEn) and atrial fibrillatory rate (AFR) are the useful tools for evaluation of atrial electrophysiological properties. Heart rate variability (HRV) is a good indicator for cardiac autonomic function. We aimed to evaluate atrial activity by SampEn and AFR correlated with HRV in AF patients with acute ischemic stroke compared to which in AF patients with previous ischemic stroke.

Methods and Results: Patients (age 69±10 years, n=40) were recruited, thereafter HRV, AFR, and SampEn were analyzed from surface electrocardiogram (ECG). Acute stroke group showed significant decreases in standard deviation of normal-to-normal intervals (SDNN), normalized low frequency (LF) and high frequency (HF) power (138±36 ms vs. 170±61 ms, 13±4 vs. 18±8 and 34±8 vs. 46±15, respectively) compared to post-stroke group. However, there was no significant difference in the LF to HF power (LF/HF) ratio between these two groups (0.41±0.14 vs. 0.43±0.24). Moreover, SampEn did not alter after stroke recovery, while AFR tended to decrease.

Conclusions: Atrial electrophysiology properties by SampEn and AFR are not influenced by cardiac autonomic derangement during acute ischemic stroke period.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia associated with an increased risk of ischemic stroke.[1] The prevalence of AF is 5 per 100,000 populations in Thailand.[2] The mortality risk due to systemic embolization related to AF including ischemic stroke increases to 1.5-1.9 compared to healthy populations in the same age group.[3] On the other hand, about 15-21% of acute ischemic stroke patients have AF.[4] Cardiac monitoring with 24-hours electrocardiography (ECG) to screen for AF is recommended in standard guidelines for acute stroke management.[5]

There are several postulated mechanisms of AF occurrence.[6] One of the widely accepted theories of AF genesis is about an inhomogeneity of electrical signals in atrial chamber.[6-8] These signals propagate in an irregular pattern called multiple reentry which consists of several reentrant circuits, and a chance of these reentrant circuits to convert into normal sinus rhythm (NSR) is inversely proportional to the number of reentrant waves in atrial wall.[6-8] Many researchers have explored the relationship between an irregularity of AF electrical signal pattern (AF complexity) and the number of reentrant waves in atrial chamber by applying signal processing techniques to surface electrocardiogram (ECG) analysis.[9] This could be done by using specific algorithms, which may be spectral analysis (atrial fibrillatory rate or AFR) or non-linear analysis (sample entropy or SampEn) to transform the atrial signals for AF pattern characterization.[8] SampEn is a good regularity

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estimator of atrial activity in AF.[10] Currently, these novel biosignals have been used to predict AF recurrence after treatment with direct current shock by external electrical cardioversion (ECV) as well as predict the behavior of paroxysmal AF (PAF).[7,8,10]

It has been known that heart rate variability (HRV) reflects cardiac autonomic function.[11] The analysis of HRV provides useful information about disturbances in autonomic regulation in several cardiac diseases including AF.[12] Cardiac autonomic dysfunction is commonly found in patients with ischemic stroke.[13-15] HRV has already been used with promising results in the assessment of the autonomic impairment associated with acute stroke.[16] The reduced HRV was found in acute ischemic stroke[17] as well as chronic AF[18], and lower values of the standard deviation of normal-to-normal R wave to R wave (RR) intervals or SDNN were independent predictors of an unfavorable functional outcome after ischemic stroke.[14] Cardiac autonomic function plays a crucial role in initiation and perpetuation of AF.[19] Interaction between autonomic innervation and atrial myocytes is related with generation of ectopic activities.[20] Atrial ectopic beats are the important mechanisms in AF patients.[21] Effect of autonomic changes might show up in atrial activity analyzed by SampEn. Also, autonomic changes might affect AFR.

We aimed to evaluate atrial activity by SampEn and AFR correlated with HRV in AF patients with acute ischemic stroke compared to which in AF patients with previous ischemic stroke to test whether cardiac autonomic derangements relate to AF signal complexity in acute ischemic stroke.

METHODS

Study populations and ECG measurements

This study enrolled a total of 40 subjects (age 40-80 years) including 20 AF patients with acute ischemic stroke episode and 20 AF patients recovering from ischemic stroke (post-stroke). The study has been carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association. Patient care followed appropriate standard of Human Ethics Committee, Faculty of Medicine, Thammasat University.

The ECG recordings were acquired with a sampling rate of 1000 Hz using lead II and V1 for 5-minute long duration within 24 hours after admission for acute stroke patients or during the follow-up visit (with a cut-off of up-to-one-month duration after discharge) at the outpatient department for post-stroke patients. These two groups of patients were individually matched with respect to age (i.e. $\leqslant$44, 45-54, 55-64, 65-74, and $\geqslant$75 years), gender, as well as the remaining $CHADS_2$ criteria (cardiac failure or dysfunction, hypertension, and diabetes mellitus). The matching factors were selected because of their known effect on AF and stroke risk. All recordings were made in similar conditions with subjects maintained at rest and in a comfortable position. The ECG recording files were further tested in a blinded fashion. All subjects gave their written informed consent to participate in the study which was approved by the local Ethical Committee.

ECG analysis: Atrial Fibrillatory Rate and Sample Entropy

Regarding the analysis of surface ECG from AF patients, the most prominent atrial signals (in lead V1) are usually selected for both AFR and SampEn analysis.[10,22] AFR has been shown to have relation with atrial fibrillatory cycle length or an index of atrial action potential refractoriness and AF organization.[23] This biosignal correlates and also estimates the results of AF treatment with antiarrhythmic drugs or cardioversion.[23] SampEn is a tool to examine a time series for similar epochs and assigns a non-negative number to the sequence, with larger values corresponding to more irregularity in the data.[10] Similar to AFR, this parameter could be applied to test atrial activity organization in AF from surface ECG, and shows benefits in classification between terminating and non-terminating PAF episode as well as predicts outcome of ECV in persistent AF patients.[7, 9]

ECGs from standard digital ECG recording system (sampling rate of 1000 Hz, 5-minute long) were analyzed using software algorithms modified by our group. The main structure of the algorithms used in our software program has been applied from those previously developed by Alcaraz *et al*[10] and Bollmann *et al.*[23] Briefly, TQ interval or atrial signals without ventricular activities were extracted from at least 1-min long ECG by QRS-T complex cancellation technique (Figure 1). Thereafter, spectral analysis was applied to create power spectrum of 10-second long consecutive TQ interval (remainder ECG) by fast Fourier transform (FFT), then the atrial fibrillatory frequency (in Hz) was identified from the highest spectral peak and turned into AFR in fibrillations per minute or fpm by multiplying with

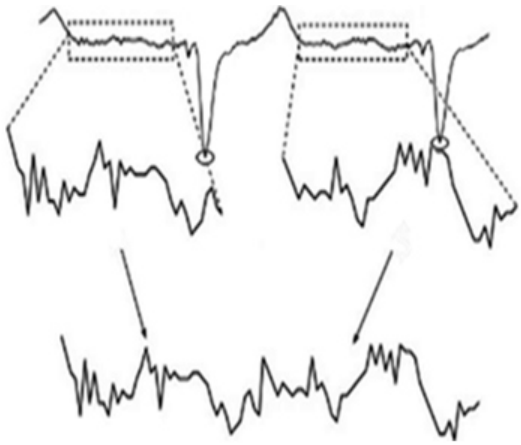

Figure 1. Diagram for signal processing method to acquire TQ interval. A representative for TQ interval or atrial signals without ventricular activities, which were extracted from ECG by cancellation of QRS-T complex, was demonstrated before being proceeded to further analysis. (Reproduced from Alcaraz R, Rieta JJ. (2010)[10], used with permission)

60. Finally, SampEn analysis was also performed on the same 10-second long consecutive TQ interval mentioned above.

Heart Rate Variability

The standard procedure and interpretation of HRV analyses was defined in 1996 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).[24] The time domain measures of HRV most commonly reported within the literature consist of standard deviation of normal-to-normal (NN) intervals (SDNN), root mean square of successive differences between NN intervals (rMSSD), and proportion of successive NN intervals greater than 50 ms (pNN50).[25] It has been known that SDNN represents total HRV while beat-to-beat changes in RR intervals (rMSSD as well as pNN50) are considered a reflection of vagal outflow.[25] For frequency domain measures of HRV, they are categorized into high, low, and very low frequency power ranges or HF, LF, and VLF, respectively. HF is equivalent to the respiratory sinus arrhythmia and represents vagal control of the heart. LF is a joint contribution by both vagal and sympathetic nerves, while the low-frequency to high-frequency power (LF/HF) ratio is considered to reflect sympathovagal balance.[16] Most studies of HRV have used 24 hour Holter recorded ECGs, which is often not feasible, and may be unnecessary. Therefore, the use of five minute recordings or standard short-term HRV analysis has been proved for its stability and consistency with time.[26,27] In this study, we used commercial standard program software (LabChart®, HRV module) for analysis of short-term HRV.

Statistical analysis

Values are expressed as mean $\pm$ standard deviation, and compared between groups using Student's t-test for continuous variables and χ^2 test or Fisher's exact test for categoric variables. Bivariate correlation between SampEn, AFR and HRV variables was performed using Pearson's correlation coefficients. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The demographic data from acute stroke and post-stroke patients are presented in Table 1. There were no significant differences in any clinical patient characteristics between acute stroke and post-stroke group, including number of patients with insular-involvement ischemic stroke. However, among all medication uses, post-stroke patients had significantly higher percent of drug using only statins and anticoagulants compared to acute stroke group (Table 1). Baseline HRV findings in time domain of the patients are summarized in Table 2. Patients in acute stroke group showed significantly higher heart rate but lower values of SDNN than those in post-stroke group (Table 2). The LF and HF power in normalized units (n.u.) were displayed in Figure 2. Both LF and HF in post-stroke patients (18 $\pm$ 8 n.u. and 46 $\pm$ 15 n.u., respectively) were significantly higher than those in acute stroke group (13 $\pm$ 4 n.u. and 34 $\pm$ 8 n.u., respectively). For LF/HF ratio, there was no significant difference between two groups, i.e., post-stroke patients; 0.43 $\pm$ 0.24, and acute stroke patients; 0.41 $\pm$ 0.14 (Figure 3). Furthermore, AFR tended to decrease in post-stroke patients (378 $\pm$ 42 fpm) compared to those with acute stroke (406 $\pm$ 65 fpm) although there was no significant difference, while SampEn was similar in both group (0.12 $\pm$ 0.02 and 0.12 $\pm$ 0.02, respectively) as described in Figure 3.

When analyzing acute stroke and post-stroke patients together, only correlation between AFR and heart rate as well as pNN50 was significant ($R = 0.33$, $P < 0.05$; and $R = -0.33$, $P < 0.05$, respectively) as in Figure 4.

Table 1: The baseline characteristics of the patients

Characteristics	Acute stroke patients (n = 20)	Post-stroke patients (n = 20)	*P* values
Age, years	69 ± 9	68 ± 12	NS
Female, n (%)	11 (55)	11 (55)	NS
CHF, n (%)	2 (10)	1 (5)	NS
HT, n (%)	13 (65)	13 (65)	NS
DM, n (%)	5 (25)	5 (25)	NS
Vascular diseases, n (%)	2 (10)	1 (5)	NS
$CHADS_2$ score	3.4 ± 1.1	3.4 ± 0.9	NS
Insular involvement, n (%)	11 (55)	6 (30)	NS
Medications			
Beta-blocker, n (%)	4 (20)	7 (35)	NS
Calcium channel blocker, n (%)	0 (0)	3 (15)	NS
Digitalis, n (%)	0 (0)	1 (5)	NS
ACE inhibitor/angiotensin receptor blocker, n (%)	1 (5)	6 (30)	NS
Other antihypertensives, n (%)	0 (0)	4 (20)	NS
Aspirin, n (%)	6 (30)	1 (5)	NS
Anticoagulants, n (%)	3 (15)	18 (90)	< 0.01
Statins, n (%)	9 (45)	18 (90)	< 0.01

Values are mean ± S.D. or n (%). CHF, congestive heart failure; HT, hypertension; DM, diabetes mellitus; ACE, angiotensin converting enzyme; NS, not significant.

DISCUSSION

In accordance of previous studies,[13,17,28,29] our study demonstrates that major HRV parameters (both time and frequency domain), i.e. SDNN, LF, and HF, in patients during acute stroke period are significantly depressed compared with those with previous ischemic stroke. These findings confirm that derangement of cardiac autonomic function, likely concerning both sympathetic and parasympathetic nervous systems.[28] However, low frequency to high frequency power (LF/HF) ratio is not significantly different in acute stroke group as compared to previous stroke group. This may be the effect of compensation of autonomic nervous system to maintain sympatho-vagal balance.[30] Many kinds of neuromodulators may take responsible to alter autonomic phenotype in order to maintain sympatho-vagal balance in both healthy and disease conditions.[31]

Regarding AF pathophysiology, the in-depth studies in various animal AF models as well as AF clinical trials are limited and there is still inconsistent information.[32] Nevertheless, it is widely believed that AF may be triggered and sustained by either reentrant or focal electrical activity, especially by pulmonary vein (PV)

Table 2: Heart rate variability (Measures in time domain) of the patients

HRV parameters	Acute stroke patients (n = 20)	Post-stroke patients (n = 20)	*P* values
Heart rate, bpm	98 ± 12	78 ± 14	< 0.01
SDNN, ms	138 ± 36	170 ± 61	< 0.05
rMSSD, ms	194 ± 53	236 ± 84	NS
pNN50, %	73 ± 12	77 ± 9	NS

SDNN, 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; NS, not significant.

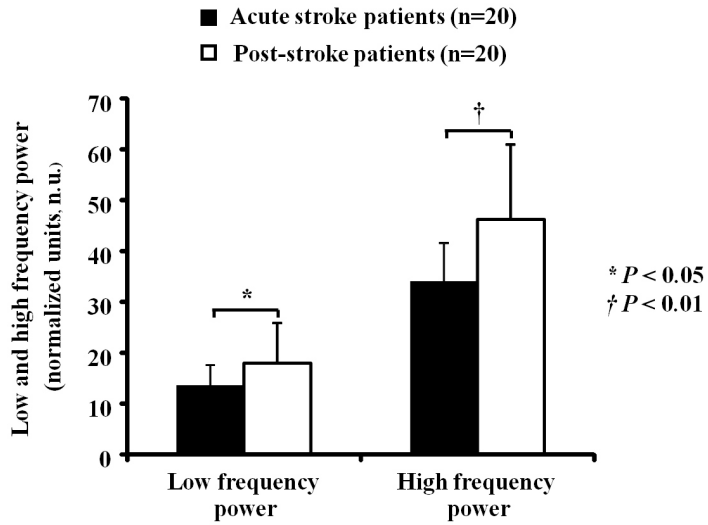

Figure 2. Low frequency (LF) power and high frequency (HF) power in normalized units (n.u.) from patients in acute and post-stroke group. *P* values are shown for the comparison between groups.

mechanoelectrical feedback.[33] The cellular studies on atrial cardiomyocytes have demonstrated that changes in function of membrane ion channels affecting transmembrane action potential as well as refractory period could lead to arrhythmia by triggered activity and/or reentry. PVs are common sites for AF initiation, then atrial remodeling occurs, which causes alterations of some ion current and proteins, for example, a decreased L-type calcium current, an increased inward rectifier current, and the changing of number or location of connexin protein. Finally, these alterations could act as the substrates for reentry and self maintenance of AF.[32] Moreover, previous studies have shown that the mechanisms relevant to autonomic abnormalities that precipitate AF are thought to be the inhomogeneous sympathetic and vagal activities that causes unequal shortening of atrial refractoriness, thus creates electrophysiological heterogeneity and reentry.[34,35] Following this assumption, cardiac autonomic dysfunction due to the differences between a degree of altered sympathetic and vagal tone in AF patients with acute stroke could lead to more

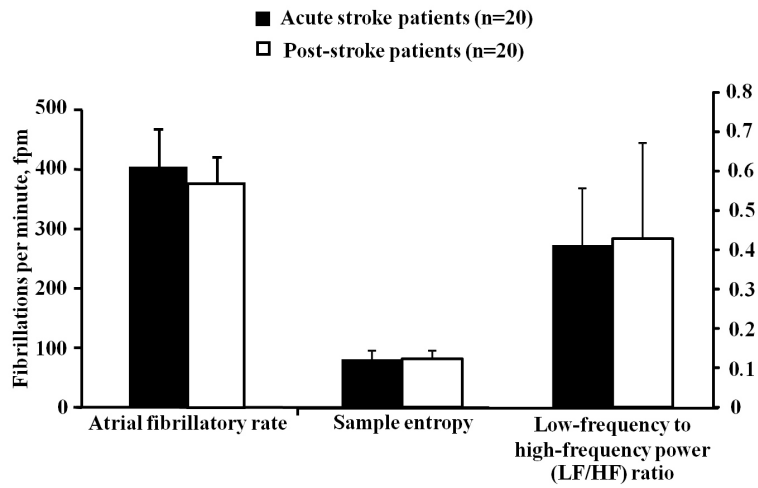

Figure 3. Atrial fibrillatory rate (AFR), sample entropy (SampEn), and low-frequency to high-frequency (LF/HF) power ratio from patients in acute and post-stroke group. Left-hand scale is for AFR, and right-hand scale is for SampEn as well as LF/HF ratio.

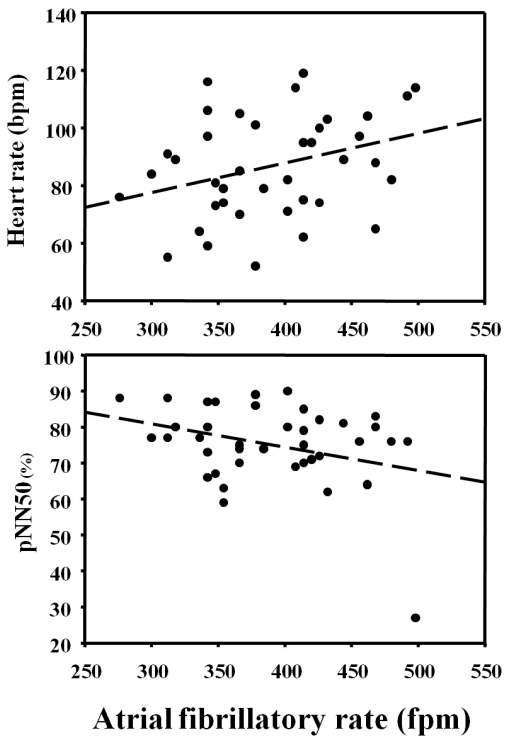

Figure 4. Scatter plot between atrial fibrillatory rate or AFR and heart rate or HR (upper panel) as well as pNN50 (lower panel) in all patients. The slope of the regression lines (dashed lines) indicate positive correlation between AFR and HR but negative correlation between AFR and pNN50 (R = 0.33, $P < 0.05$; and R = - 0.33, $P < 0.05$, respectively). 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.

complex reentry and remodeling in AF compared to those recovered from stroke. However, atrial electrophysiological property analysis by SampEn as well as AFR is not significantly different in acute ischemic stroke group as compared with those of previous stroke group in our study. There is a possibility that the balance of sympatho-vagal system may minimize effect of autonomic dysfunction to atrial components. On the other hand, it might be possible that SampEn as well as AFR is not sensitive to cardiac autonomic derangement.

There is evidence from previous studies reported that AF in patients without structural heart disease is vagally dependent whereas AF in patients with structural heart disease is sympathetically mediated.[36,37] The pNN50 component is a good representation of cardiac parasympathetic tone.[38] All AF patients in our study are non-structural heart disease. Rising AFR is inversely correlated with declining pNN50 of all patients in our study. This finding represents the close relationship between atrial activity by AFR and parasympathetic system by pNN50. If that is the case, AFR may be more sensitive than SampEn to get influenced by autonomic derangement. Furthermore, another explanation for this would be the closer relation between AFR and atrial refractoriness. It has been known that shortening of atrial refractoriness plays an important role in electrophysiological mechanism underlying reentry in AF. And the length of the averaged atrial fibrillatory cycle can be used as an index of the averaged atrial myocardial refractoriness and AF organization.[23] Therefore, the atrial fibrillatory frequency or rate acquired from spectral analysis of atrial activities (TQ intervals), which is inversely related to fibrillatory cycle length, can directly reflect refractoriness at atrial wall. While the application of SampEn in AF provides a potential index for unsynchronized atrial activities to estimate the number of active reentries rather than refractoriness within the atrial wall.[9] This could possibly explain how AFR and SampEn have direct and indirect relation to atrial refractoriness, respectively. In particular, it might be the reason for AFR as being an optimal index of AF complexity rather than SampEn.

Non-invasive characterization of AF using the surface ECG from AF patients by applications of different signal processing techniques has been considered as a very promising and useful tool towards the understanding of AF pathophysiology and prediction of therapy efficacy. In this study, no influence of cardiac autonomic derangements on AF signal complexity in acute ischemic stroke could provide evidence of good prognosis as well as the proper treatment for AF in this specific patient group.

Our study population depended on the availability of consecutive patients with specific clinical features in a limited time frame. Therefore, we decided to use matching technique for proper comparisons between acute stroke and post-stroke group to eliminate most of the confounding factors affecting AF and stroke, for example, age, gender, cardiac failure or dysfunction, hypertension, and diabetes mellitus. Nevertheless, a few medications still remain uncontrollable factors. The differences in using anticoagulant as well as statins between two groups may affect our results. The pleiotropic effects of statins, including endothelial function enhancement, and decrease in oxidative stress and

inflammation, might possibly alter the cardiac remodeling process and mask the relations between AF signal complexity and HRV in post-stroke patients found in the study. This requires further confirmation with well selected population of AF patients with ischemic stroke.

In conclusion, atrial electrophysiology properties by SampEn and AFR are not influenced by cardiac autonomic derangement during acute ischemic stroke period. Further study in different AF groups is needed to confirm this finding.

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DISCLOSURE

Conflict of Interest: None

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