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Rhythm-Independent Feature of Heart Rate Dynamics Common to Atrial Fibrillation and Sinus Rhythm in Patients With Paroxysmal Atrial Fibrillation

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Abstract

Objectives. To examine if the long-range correlation in heart rate variability is a rhythm-independent characteristic common to both atrial fibrillation (AF) and sinus rhythm (SR) periods in patients with paroxysmal atrial fibrillation (PAF).

Methods. Holter electrocardiography was analyzed during sleep in 18 patients with paroxysmal atrial fibrillation during the atrial fibrillation (PAF-AF) and sinus rhythm (PAF-SR) periods, and also in 19 healthy controls with sinus rhythm (CTR-SR). The heart rate dynamics were assessed with the power-law spectral exponent (slope) of the log-log power spectrum between 0.0001 Hz and the breakpoint frequency.

Results. The slope showed a significant correlation between PAF-SR and PAF-AF ($r = 0.614$, $p < 0.01$). During sinus rhythm, the slope in paroxysmal atrial fibrillation with cardiovascular disease [PAF-SR (cvd +)] was steeper than that in paroxysmal atrial fibrillation without cardiovascular disease [PAF-SR (cvd −)] ($p < 0.05$). Although the slope was comparable between PAF-SR (cvd −) and CTR-SR, the slope in PAF-SR (cvd +) was steeper than that in CTR-SR ($p < 0.05$). A similar tendency was shown during atrial fibrillation. The slope in paroxysmal atrial fibrillation with cardiovascular disease [PAF-AF (cvd +)] was steeper than that in paroxysmal atrial fibrillation without cardiovascular disease [PAF-AF (cvd −)] ($p < 0.05$). Although the slope was comparable between PAF-AF (cvd −) and CTR-SR, the slope in PAF-AF (cvd +) tended to be steeper than that in CTR-SR.

Conclusions. The long-range correlation in heart rate variability during sleep was a rhythm-independent characteristic and so may have a similar clinical value during atrial fibrillation and sinus rhythm in patients with paroxysmal atrial fibrillation.

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Key Words

■**Heart rate (variability)** ■**Electrocardiography (ambulant)** ■**Spectrum analysis** ■**Atrial fibrillation (paroxysmal)**

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INTRODUCTION

Heart rate variability using time and frequency domain methods is useful for evaluating the severity and prognosis of cardiovascular disease in patients with sinus rhythm (SR)[1–8], but most heart rate variability studies have not studied atrial fibrillation (AF). The changes in the R-R interval during atrial fibrillation result mainly from autonomic neural modulations of the electrophysiological properties and concealed conduction in the atria and atrioventricular node[9–11]. Rapid and random impulses result because the sinus node loses its pacemaker function during atrial fibrillation. Therefore, conventional time and frequency domain indices of beat to beat heart rate variability in atrial fibrillation differ from those in sinus rhythm. These conditions seem to preclude applications of standard heart rate variability analysis. However, some studies reported that reduced heart rate variability can be used to predict adverse prognosis of cardiovascular events in patients with atrial fibrillation[12–14].

The power spectrum of the nonharmonic and long-range component of heart rate variability during sinus rhythm shows a power law relationship, a $1/f^{\beta}$ noise-like down sloping linear pattern when plotted as log power against log frequency, suggesting an origin in a complex regulatory process[15]. In sinus rhythm, the slope in patients with cardiovascular disease is steeper than that in normal subjects[16–19] and has a close relationship with the prognosis[16,20–22]. The power spectrum of R-R intervals during atrial fibrillation showed an angular shape with a breakpoint at 0.005 ± 0.002 Hz, by which the spectrum was divided into high-frequency and low-frequency components with different spectral characteristics. The high-frequency component showed a white noise-like flat spectrum and the low-frequency component showed a $1/f^{\beta}$ noise-like power law spectrum like that in sinus rhythm[23].

The present study investigated whether the long-range correlation or slope in heart rate variability is a rhythm-independent characteristic in patients with paroxysmal atrial fibrillation (PAF).

SUBJECTS AND METHODS

Subjects

This study included 18 patients with paroxysmal atrial fibrillation (11 males, 7 females, mean age 65 ± 11 years, range 43–89 years), 6 with hypertension with left ventricular hypertrophy including 1 with controlled hyperthyroid disease, 1 with ischemic heart disease, 2 with cardiomyopathy, 1 with popliteal artery embolism, and 8 patients free of cardiovascular disease. Seven patients were medicated with digoxin, 5 with class Ia or Ic antiarrhythmic drugs and 3 with β-adrenergic blockers during atrial fibrillation, whereas 8 patients were medicated with digoxin, 5 with class Ia or Ic antiarrhythmic drugs and 2 with β-adrenergic blockers during sinus rhythm. During this trial, the clinical condition did not change during atrial fibrillation and none of the patients with paroxysmal atrial fibrillation had congestive heart failure.

Nineteen age-matched normal control subjects with sinus rhythm (CTR-SR; 6 males, 13 females, mean age 66 ± 10 years, range 49–85 years) were also studied with no evidence of heart disease detected by medical history, physical examination, electrocardiography (ECG) and chest radiography. The study was approved by the local ethical committee of Kochi Medical School and all subjects gave their written informed consent.

Data collection

All subjects were monitored for at least 24 hr with a portable ambulatory ECG recorder (Holter ECG) with modified V_1 and V_5 lead placement. The tapes were played back with a Holter ECG database system (SCM 6000, Fukuda Denshi). The data were sampled digitally and transferred to a PC for analysis of heart rate variability. QRS complexes were detected and labeled automatically. The results of the automatic analysis were reviewed, and any errors in R wave detection and QRS labeling were edited manually. Holter ECG was performed twice in patients with paroxysmal atrial fibrillation, during sinus rhythm (PAF-SR) and atrial fibrillation (PAF-AF) periods. Each time series of R-R intervals during sinus rhythm and atrial fibrillation was visually inspected for appropriate editing. The mean interval between the recordings was 4 months. Nine patients were in atrial fibrillation for the first recording and the others were in sinus rhythm. The duration of paroxysmal atrial fibrillation was 19 ± 7 hr. The R-R interval variability and spectral characteristics were evaluated for 5 hr during sleep (22: 00 p.m.–3: 00 a.m.) to exclude the influence of physical activities. Awake and sleep

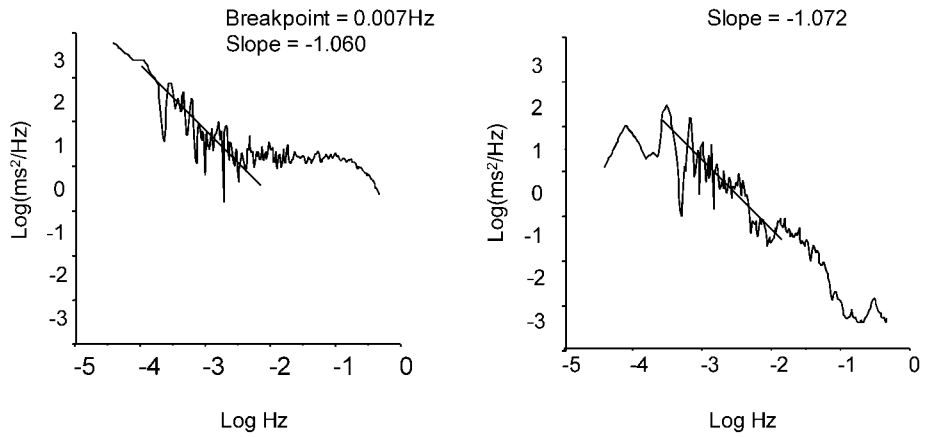

Fig. 1 Representative examples of power spectra and power-law slopes during sleep in a patient with paroxysmal atrial fibrillation
Left: Spectrum during atrial fibrillation.
Right: Spectrum during sinus rhythm.

times were evaluated from the diary entries. All data of the patients and normal subjects showed premature contraction, noise or artifacts in less than 5% of total QRS complexes.

The patients with paroxysmal atrial fibrillation were divided into two subgroups according to the presence(10, cvd＋)or absence(8, cvd－)of cardiovascular disease. The R-R interval variability and spectral characteristics were compared between these subgroups, and with CTR-SR.

Analysis of heart rate variability and spectral characteristics

Spectral analysis used the method described previously[23]. Briefly, the spectral exponent of the R-R interval power spectrum was evaluated by plotting log power spectral density against log frequency. The log frequency axis was divided into 60 equally spaced bins/decade, *i.e.*, 307 bins 0.0167 log(Hz) wide. Log power spectral density was averaged for each bin; the values for bins without data points in the lower frequency range were obtained by interpolation. Linear regression analysis was performed for the averaged log power spectral density and log frequency data of the bins within the frequency bands of interest. When plotted as log power spectral density against log frequency, the data of atrial fibrillation showed an angular shape with a breakpoint by which the spectrum was separated into two different structures; a linear down sloping structure below the breakpoint and a flat horizontal structure above the breakpoint. Therefore, the slope during sinus rhythm in patients with paroxysmal atrial fibrillation was measured from 10^{-4}Hz to this breakpoint frequency. The slopes of control subjects were calculated from 10^{-4}Hz to the mean breakpoint frequency during atrial fibrillation in patients with paroxysmal atrial fibrillation(0.005 Hz). Mean R-R interval(msec)and standard deviation(msec) were also calculated with the same data as used to calculate the slope.

Statistical analysis

The data are presented as mean ± SD. ANOVA was used to assess the differences between patients with paroxysmal atrial fibrillation and the control subjects. A post hoc analysis for comparisons was performed by Fisher's procedure. Differences of spectral characteristics between atrial fibrillation and sinus rhythm in patients with paroxysmal atrial fibrillation were assessed by the paired *t*-test, and the relationship of the data between paroxysmal atrial fibrillation and sinus rhythm were assessed by Pearson's correlation coefficients. p value < 0.05 was considered statistically significant.

RESULTS

The breakpoints during PAF-AF were in the range 0.0009－0.01 Hz(mean 0.005 ± 0.004 Hz). Representative example of power-law slopes in PAF-AF and PAF-SR during sleeping are shown in **Fig. 1**. The spectrum during PAF-AF showed an angular shape with the breakpoint of 0.007 Hz. The spectrum showed a linear down sloping structure

below the breakpoint and a flat horizontal structure above the breakpoint. The slope for lower frequencies between 0.0001 Hz and 0.007 Hz was −1.060. In contrast, the spectrum during PAF-SR showed a monotonous linear down sloping structure and the slope was −1.072 in the same frequency range as during PAF-AF.

Comparison between patients with paroxysmal atrial fibrillation and control subjects with sinus rhythm

There was no significant difference in the slope, mean R-R interval and standard deviation between PAF-SR and CTR-SR, whereas standard deviation in PAF-AF was significantly larger than that in CTR-SR(**Table 1**). The slope in PAF-SR(cvd+) was significantly steeper than that in CTR-SR, and that in PAF-AF(cvd+)tended to be steeper than that in CTR-SR. Mean R-R interval and standard deviation in PAF-SR(cvd−)were significantly larger than those in CTR-SR. Mean R-R interval in PAF-AF(cvd−)was significantly smaller, and standard deviation was larger than that in CTR-SR (**Table 2**).

Comparison between PAF-AF and PAF-SR

Mean R-R interval in PAF-AF was smaller than that in PAF-SR, and standard deviation in PAF-AF was larger than that in PAF-SR. However, there was no significant difference in the slope between PAF-SR and PAF-AF(**Table 1**). In the same subgroup of rhythm, the slopes in PAF-SR(cvd+)and PAF-AF(cvd+)were significantly steeper than those in PAF-SR(cvd−)and PAF-AF(cvd−), respectively(**Table 2**, **Fig. 2**). In the same subgroup of cardiovascular disease, the mean R-R interval in PAF-AF(cvd−)was significantly smaller than that in PAF-SR(cvd−). Standard deviation in PAF-AF(cvd+)was significantly larger than that in PAF-SR(cvd+)(**Table 2**).

Correlation between PAF-AF and PAF-SR

The slope between PAF-AF and PAF-SR was correlated significantly($r = 0.614$, $p < 0.01$), but there was no significant correlation between the other indices(**Table 3**, **Fig. 2**).

DISCUSSION

The main finding of this study was that the long-range correlation in heart rate variability, the slope, was a rhythm-independent characteristic common to both atrial fibrillation and sinus rhythm during sleep in patients with paroxysmal atrial fibrillation. This result indicates that the analysis of heart rate variability may have similar clinical value in both atrial fibrillation and sinus rhythm in patients with paroxysmal atrial fibrillation.

Table 1 Comparison between control subjects and patients with paroxysmal atrial fibrillation during sinus rhythm and atrial fibrillation

	CTR-SR (n=19)	PAF-SR (n=18)	PAF-AF (n=18)
Slope	−1.185±0.237	−1.297±0.323	−1.13±0.272
Mean R-R interval (msec)	949±101	1,039±215	850±228†
Standard deviation(msec)	83±21	105±51	180±60**††

Values are mean±SD.
$^{**}p<0.01$: Mean is significantly different from CTR-SR.
$^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$: Mean is significantly different from PAF-SR.
CTR-SR=control subjects during sinus rhythm; PAF=paroxysmal atrial fibrillation; PAF-SR=patients with PAF during sinus rhythm; PAF-AF=patients with PAF during atrial fibrillation.

Heart rate variability in atrial fibrillation

Heart rate variability is a useful tool to evaluate the severity and prognosis of cardiovascular disease[1−8]. Recently, nonlinear methods of fractal and chaos analysis were shown to be as useful or better than the linear methods of time and frequency domain analysis[16−22,24,25]. However, patients with atrial fibrillation were excluded from most of these studies. Heart rate variability analysis in patients with atrial fibrillation was studied using standard and nonlinear analysis[12−14]. Twenty-four-hour heart rate variability was examined in 21 patients with chronic atrial fibrillation due to nonischemic mitral regurgitation, and found that reductions in time-domain measurements of ultra-low- and high-frequency components were significant predictors of the combined risk of mortality or mitral valve replacement surgery, although none of the measures predicted mortality[12]. Evaluation of 24-hour heart rate variability in 35 advanced heart failure patients with chronic atrial fibrillation found that reduced standard deviation of the 5-minute mean R-R interval was the only independent predictor of event-free survival[13]. Recently the reduction of ventricular response irregularity measured by the nonlinear method, *e.g.* Shannon entropy and

Table 2 Slope and R-R interval of control subjects and patients with paroxysmal atrial fibrillation with or without cardiovascular disease

	CTR-SR	PAF-SR		PAF-AF	
		cvd−	cvd+	cvd−	cvd+
	(n=19)	(n=8)	(n=10)	(n=8)	(n=10)
Age (yr)	66±10	68±12	63±10	68±12	63±10
Slope	−1.185±0.237	−1.121±0.26	−1.439±0.307*†	−0.985±0.258	−1.246±0.233†
Mean R-R interval (msec)	949±101	1,089±221*	1,000±213	821±221$^{*\#}$	874±242
Standard deviation (msec)	83±21	129±45**	85±48	172±54**	187±66$^{\#\#}$

Values are mean±SD.

$^{*}p<0.05$, $^{**}p<0.01$: Mean is significantly different from CTR-SR. $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$: Mean is significantly different from patients with PAF without cardiovascular disease (cvd−) in the same rhythm. $^{\#}p<0.05$, $^{\#\#}p<0.01$: Mean is significantly different from PAF-SR (cvd−) or PAF-SR (cvd+) in each subgroup.

cvd+ = patients with PAF and cardiovascular disease; cvd− = patients with PAF without cardiovascular disease. Other abbreviations as in Table 1.

approximate entropy, using 24-hour Holter monitoring was associated with increased long-term cardiac mortality in patients with chronic atrial fibrillation[14]. These studies showed linear or nonlinear indices were independently associated with the severity and prognosis in patients with atrial fibrillation as well as in sinus rhythm, but there was no common index in both groups of our patients. According to our results, the slope during sleep corresponding to quite long heart rate variability could be a common index in both groups to assess the severity of cardiovascular disease in a mixed population of atrial fibrillation and sinus rhythm, at least in patients with paroxysmal atrial fibrillation.

The R-R intervals of atrial fibrillation are mainly determined by the functional refractory periods of the atrioventricular node, and the summation or inhibition of stimulatory pulses in the atrioventricular node. The short-term heart rate variability in patients with atrial fibrillation was white noise-like fluctuation[23]. Therefore, frequency domain indices are not useful for comparison between the sinus rhythm and atrial fibrillation periods.

Possible mechanism of heart rate variability in atrial fibrillation

The breakpoint during PAF-AF in the present study showed similar values in chronic atrial fibrillation[23], which may indicate that the breakpoint is not influenced by the duration of atrial fibrillation. Although a down sloping linear pattern was reported at lower frequency ($<0.005\pm0.002$ Hz) levels of heart rate variability in patients with chronic atri-

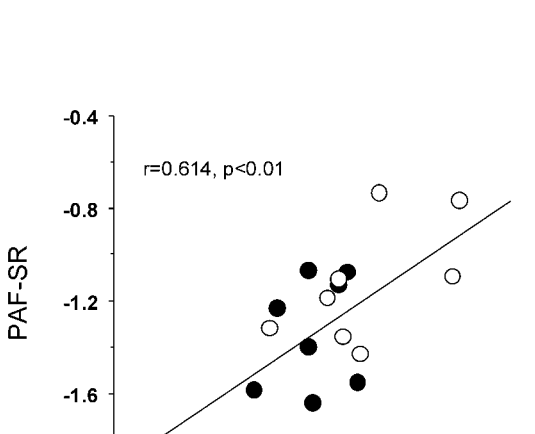

Fig. 2 Correlation of the slope between atrial fibrillation (PAF-AF) and sinus rhythm (PAF-SR) in patients with paroxysmal atrial fibrillation

Open circle: Patients with paroxysmal atrial fibrillation without cardiovascular disease. Solid circle: Patients with paroxysmal atrial fibrillation and cardiovascular disease.

Abbreviations as in Table 1.

Table 3 Correlation of spectral characteristics between atrial fibrillation and sinus rhythm in patients with paroxysmal atrial fibrillation

	r	p value
Slope	0.614	0.0067
Mean R-R interval	0.354	0.1491
Standard deviation	0.053	0.8358

al fibrillation[23], the origin of the down sloping power law spectrum with a spectral exponent of −1 ($1/f^{\beta}$ type noise) is still unknown. The regulation of heart rate variability in patients with atrial fibrillation may have two different mechanisms; long-term and short-term regulation. In short-term regulation, the white noise-like power law relationship may reflect irregularity in the atrial activity during atrial fibrillation[23]. During sinus rhythm, the long-term heart rate variability may reflect physical activity under the influence of autonomic nerve system, humoral regulation, body temperature regulation, and sleep[4]. Furthermore, the slope is altered by the patient's condition, such as aging, sleep, postural change, cardiac denervation or left ventricular function[16−18,26−30]. Examination of the relationship between heart rate variability and body movements for 7 days in healthy subjects found that $1/f^{\beta}$ type spectra in heart rate variability and body movements were at ultradian frequencies and a coherent relationship was seen only at ultradian as well as circadian frequencies[30]. Investigation of the slope in patients with myocardial infarction showed that the value of the slope in the range of 10^{-4} and 10^{-2} was close to −1 during the day and night in patients with normal left ventricular function, but was significantly more negative in patients with reduced ejection fraction[17]. In our study, the slope did not differ between PAF-SR and PAF-AF during sleep and correlated significantly in sinus rhythm and atrial fibrillation. However, the slope in patients with cardiovascular disease was significantly steeper than that in patients without cardiovascular disease during both sinus rhythm and atrial fibrillation. These results indicate that factors other than physical activity may affect the long-range correlation in heart rate variability in cardiovascular disease, both in PAF-SR and PAF-AF.

Limitations

The patient population in this study was small and heterogeneous. However, the clinical conditions were the same and the data were measured during sleep to avoid circadian variations of physical activity. The lowest frequency of our data length during 5 hr sleep was 5.6×10^{-5}Hz. The slope calculated from 10^{-4}Hz to the breakpoint was included in the frequency range. However, the slope using 24 hr data containing circadian variations of R-R interval may be different from our results. Although the slope during paroxysmal atrial fibrillation was significantly correlated with that of during sinus rhythm, nine patients with paroxysmal atrial fibrillation received different medication during PAF-AF and PAF-SR. Therefore, the effects of medication on the slope should be considered. Moreover, our results can be applied to patients with paroxysmal atrial fibrillation, but not to patients with chronic atrial fibrillation. Further study is required to evaluate the effect of medication using 24 hr or longer data of heart rate variability, and to evaluate the usefulness of the slope in patients with chronic atrial fibrillation.

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要　約

心房細動および洞調律に共通する調律によらない心拍変動要素: 発作性心房細動における検討

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目　的: 心拍変動は心血管疾患において重症度評価や予後予測に有用であるが，心房細動患者はその評価から除外されてきた．しかし，心房細動時にも洞調律時と同様な低周波領域におけるパワー則関係，すなわち，$1/f^{\beta}$ゆらぎを持つスペクトルの傾きが認められることが報告されている．この傾きが調律に依存するか否かを発作性心房細動患者で検討した．

方　法: 発作性心房細動患者18例の心房細動時(PAF-AF)および洞調律時(PAF-SR)のホルター心電図記録より睡眠時5時間を解析し対比した．また，対照として健常者19例(CTR-SR)で同様の解析を行った．傾きは対数表示したパワースペクトルより0.0001Hzから変曲点までを求めた．

結　果: 傾きはPAF-SRとPAF-AFで有意な相関を示した($r = 0.614$, $p < 0.01$)．洞調律時での比

較では，心血管病変を持つ発作性心房細動症例［PAF-SR（cvd＋）］の傾きは，持たない症例［PAF-SR（cvd－）］より急峻であった（$p < 0.05$）．また，PAF-SR（cvd－）とCTR-SRには差がなかったが，PAF-SR（cvd＋）の傾きはCTR-SRより急峻であった（$p < 0.05$）．同様の傾向が心房細動時にも認められ，PAF-AF（cvd＋）の傾きはPAF-AF（cvd－）ものより急峻であった（$p < 0.05$）．また，PAF-AF（cvd－）とCTR-SRには差がなかったが，PAF-AF（cvd＋）の傾きはCTR-SRより急峻な傾向を認めた．

結　語：発作性心房細動患者において，スペクトルの傾きは調律に依存しない．また，心房細動例でもこの傾きは洞調律例と同じく臨床的意義を持つ可能性がある．

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