

Original Article

Biological rhythm in 1/f fluctuations of heart rate in asthmatic children

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ABSTRACT

Background: The 1/f fluctuations of heart rate (HR) have been used as a novel index of autonomic function from a chronobiological viewpoint. The autonomic function of asthma sufferers differs from that of normal children. Therefore, we investigated whether there are 1/f fluctuations in asthmatic children during an asthma attack and whether asthmatic children have a different rhythm of 1/f fluctuations in the 24 h after an asthma attack.

Methods: We recorded 24 h electrocardiographs of eight asthmatic children (three females, five males; median age 8.5 years; range 7–11 years) at the time of an asthma attack and during a non-attack period and examined the 1/f^β fluctuations on HR and its rhythm over a 24 h period using the MemCalc system (GMS, Tokyo, Japan). The 1/f fluctuations on HR were calculated by the expression on a log₁₀(frequency)–log₁₀(power density) scale of the HR variability.

Results: The values of β (1/f^β fluctuations of HR) for asthma attack and non-attack periods were 0.9 ± 0.07 and 0.96 ± 0.08, respectively (*t* = 1.59; *P* = 0.13). During the asthma attack period, the rhythm was median 7.9 h (range 6.1–11.1 h), compared with 22.7 h (range 12.2–36.4 h) during the non-attack period (*t* = 0; *P* < 0.001).

Conclusion: During an asthma attack, the rhythm of 1/f fluctuations is ultradian (cycle length under 20 h),

compared with various rhythms during a non-attack period. In future, we will clarify the relevance of the ultradian rhythm of 1/f fluctuations over a 24 h period and the biological life-support system at a point of time of an asthma attack.

Key words: asthmatic children, biological rhythm, circadian rhythm, 1/f fluctuations, heart rate variability, MemCalc system.

INTRODUCTION

The 1/f fluctuations were first found in 1925 in an electric current passing through a vacuum tube.¹ Later, Musha *et al.*² reported 1/f fluctuations of heart rate (HR) in humans. These HR 1/f fluctuations are a case of 1/f^β fluctuations with β ≠ 1. The fluctuations are calculated by the expression on a log₁₀(frequency)–log₁₀(power density) scale of heart rate variability (HRV). The 1/f fluctuations of HR have been used as a novel index of autonomic function from a chronobiological viewpoint.³ For example, a decrease in the 1/f fluctuations of HR has been observed before sudden death due to ischemic heart disease or severe cardiac arrhythmia.⁴ Moreover, Otsuka *et al.*⁵ reported that the 1/f fluctuations of HR have a circadian rhythm in healthy subjects. It is possible that the presence of 1/f fluctuations of HR maintains the stability of the biological life-support system.

Although we have reported that HRV values in asthmatic children differ from those of non-asthmatic children,⁶ little is known about the 1/f fluctuations of HR in asthmatic children. We performed the present study to determine whether there are 1/f fluctuations in asthmatic children during an asthma attack and whether asthmatic

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children who have had an asthma attack have a different rhythm of 1/f fluctuations over the following 24 h period. From this study, we will consider the influence of an asthma attack on the biological life-support system.

METHODS

Subjects

Eight patients (three females, five males; median age 8.5 years; range 7–11 years) with asthma were enrolled into the study (Table 1). Asthma was diagnosed by clinical progression, measurement of serum IgE values and detection of allergens. Six patients had moderate disease and two had severe disease. The grade of severity in each of the eight cases was determined according to the guidelines of the Japanese Society of Pediatric Allergy and Clinical Immunology.⁷

We obtained 24 h electrocardiograms (ECG) when each child had been free of an asthma attack for at least 2 weeks and when each child was in our hospital because of an asthma attack. The grade of asthma attack was moderate in all cases. During a non-attack period, all patients were on oral theophylline (12–16 mg/kg per day) and a β_2 -adrenergic receptor agonist. The two children with severe asthma were on regular inhalation of beclomethasone dipropionate. In hospital, an intravenous drip injection of aminophylline (0.7 mg/kg per h) and inhalation of β_2 -adrenergic receptor agonist three times a day was administered. Consent for performing all studies was obtained from each child or his or her parents.

Processing of the 24 h ECG

We obtained an ECG from each subject over a 24 h period using a two-channel Holter recorder (SM-29 or SM-30; Fukuda-Denshi, Tokyo, Japan). Channel 1 recorded the thorax V5 induction and channel 2 recorded the V1 induction. We analyzed the data using a computer-based system (SCM 3000; Fukuda-Denshi). The RR interval, the interval between the R waves of the ECG, was measured with an interval counter using a built-in analog-to-digital converter with an interval resolution of 8 msec. The data were transferred to a personal computer (Lavie N; NEC, Tokyo, Japan) and stored on floppy disk.

MemCalc system

We analyzed the data for each subject with a MemCalc system (GMS, Tokyo, Japan). The MemCalc system is the method proposed by Ohtomo and Tanaka.⁸ It is a linearized version of the non-linear least squares method for fitting analysis in the time domain, combined with the maximum entropy method for spectral analysis in the frequency domain. We categorized the HRV power spectrum into the following components: (i) high frequency (HF; 0.15–0.6 Hz); (ii) low frequency (LF; 0.04–0.15 Hz); (iii) very low frequency (VLF; 0.003–0.04 Hz); and (iv) ultra low frequency (ULF; 0.0001–0.003 Hz).

The 1/f fluctuations of HR

The 1/f fluctuation is the slope of $\beta \neq 1$ of $1/f^\beta$ fluctuations (Fig. 1). The slope of $1/f^0$ fluctuations ($\beta \neq 0$) is

Table 1 Clinical profiles of study subjects

Case no.	Sex	Age (years)	Asthma severity	Total IgE (IU/mL)	Therapy		Concentration of theophylline (ng/mL)	
					Non-attack	Attack	Non-attack	Attack
1	F	7	Moderate	576	A + To + β_o	A + Td(0.7) + β_i	7.8	9.8
2	F	7	Moderate	164	A + To + β_o	A + Td(0.7) + β_i	9.3	11
3	M	8	Moderate	1843	A + To + β_o	A + Td(0.7) + β_i	4.1	6.1
4**	M	8	Moderate	2965	A + To + β_o	A + Td(0.7) + β_i	ND	14.4
5*	M	9	Moderate	419	A + To + β_o	A + Td(0.7) + β_i	12.6	8.9
6	F	9	Moderate	437	A + To + β_o	A + Td(0.7) + β_i	ND	9.3
7*	M	7	Severe	1018	A + To + β_o + Si	A + Td(0.7) + β_i	10.6	11
8	M	11	Severe	203	A + To + β_o + Si	A + Td(0.8) + β_i	11	12.3

*Uncalculated rhythm for the non-attack period.

**Uncalculated rhythm for the attack period.

A, anti-allergics; To, Oral theophylline; β_o , oral β_2 -adrenergic receptor agonist; Si, inhaled steroid; Td(X), intravenous theophylline (X mg/kg per h continuously); ND, not done.

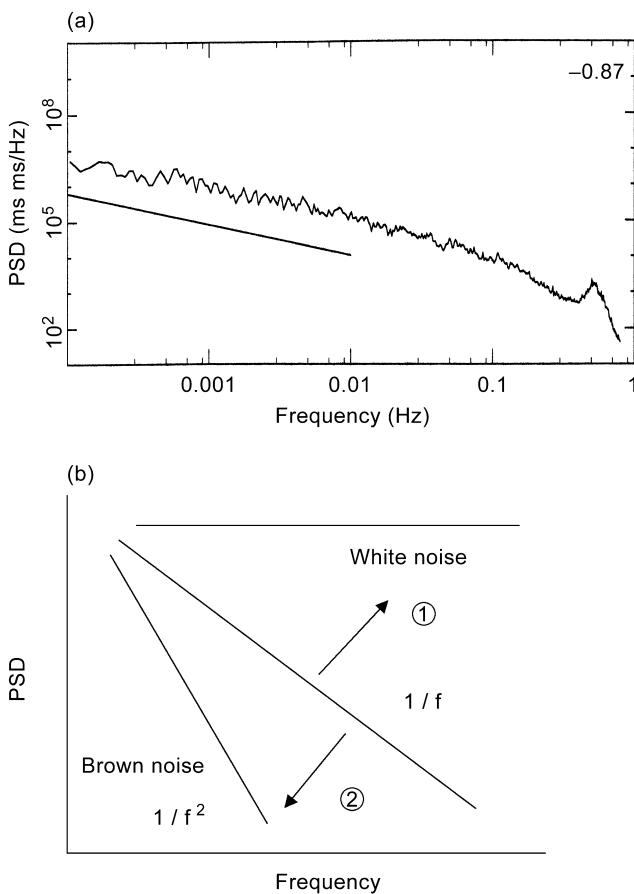


Fig. 1 Schema of the slope of $1/f^\beta$ fluctuations of heart rate (HR). (a) The slope of $1/f^\beta$ fluctuations from 0.0001 to 0.01 Hz. (b) Relationships between $1/f^\beta$ fluctuations and noise. The mid-line is the slope $1/f$ fluctuations. The arrow at ② shows a shift to the slope of $\beta \neq 0$ ($1/f^\beta$ fluctuations of HR) and the slope of $\beta \neq 0$ is called white noise. The arrow at ①, shows a shift to the slope of $\beta \neq 2$ and the slope of $\beta \neq 2$ is called brown noise. PSD, power spectral density.

called ‘white noise’ and the slope of $1/f^2$ fluctuations ($\beta \neq 2$) is ‘brown noise’. The $1/f$ fluctuations have been determined in healthy people by analysis of HRV.⁵ For the analysis of $1/f$ fluctuations of HR, the power spectral band was focused on the range from ULF to LF, or from 0.0001 to 0.01 Hz. We calculated the slope of the $1/f$ fluctuations of HR by the expression on a $\log_{10}(\text{frequency})$ – $\log_{10}(\text{power density})$ scale; that is, we calculated the slope of the regression line between the \log_{10} of frequency between 0.0001 and 0.01 Hz and the \log_{10} of power density of the RR spectrum over 24 h.

Rhythms in the $1/f$ fluctuations of HR

We investigated rhythms in the $1/f$ fluctuation of HR for each subject using MemCalc/Chiram (GMS). MemCalc/Chiram is the software of the MemCalc system. We calculated each amplitude of the $1/f$ fluctuation at intervals of 5 min for the 24 h ECG record and fitted it to curves of trigometric function expressed by:

$$X(t) = A_0 + \sum_{n=1}^{N_p} A_n \cos(2\pi f_n(t + \theta_n))$$

where $X(t)$ is a discrete time series at $t = k\Delta t$ ($k = 1, 2, 3, \dots$), where k is the length of the time series and Δt is the sampling time interval. The f_n ($= 1/T_n$; where T_n is the cycle of curves of trigometric function), A_n and θ_n are the frequency, amplitude and the phase shift of the n th periodic component, respectively, and A_0 is the average value of the time series. N_p is the total number of components.

We used the reciprocal number ($1/T_n$) for the highest amplitude (f_n) of some amplitudes as ‘rhythm’ during the day in the $1/f$ fluctuation of HR.

Statistical analysis

We compared the slope of the $1/f$ fluctuation during an asthma attack and during a non-attack period in eight asthmatic children. Rhythms in the $1/f$ fluctuations were also compared. When the values were distributed normally, we used a paired-sample t -test. Results are reported as the mean \pm SD.

When values were not distributed normally, data for the two periods were compared using the Wilcoxon test. Results are reported as medians. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The $1/f$ fluctuations of HR

The $1/f$ fluctuations of HR during an asthma attack and during a non-attack period is shown in Fig. 2. The values of β ($1/f^\beta$ fluctuations of HR) during an asthma attack and during a non-attack period were 0.9 ± 0.07 and 0.96 ± 0.08 , respectively. These values were not significantly different ($t = 1.59$; $P = 0.13$). All values for the subjects were within the normal range (0.8–1.2).

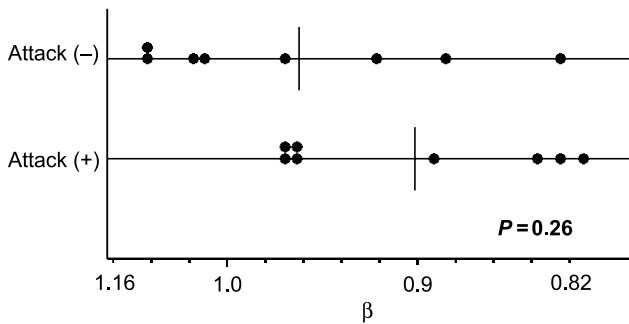


Fig. 2 1/f fluctuations of heart rate (HR) for asthmatic children. The horizontal axis shows values of β ($1/f^\beta$ fluctuations of HR). Attack (-), non-attack period; attack (+), during an asthma attack.

Rhythms in the 1/f fluctuations of HR

Rhythms in the 1/f fluctuations of HR during an asthma attack and during the non-attack period are shown in Fig. 3. During the asthma attack and non-attack periods, the rhythms were of a median 7.9 h (range 6.2–11.1 h) and 22.7 h (range 12.2–36.4 h), respectively ($t = 0$; $P < 0.001$). Data for two subjects (cases 5 and 7) during the non-attack period and data for one subject (case 4) during an asthma attack were not included when calculating the rhythms of the 1/f fluctuations because their rhythms could not be analyzed using the MemCalc/Chiram system. Although rhythms in the 1/f fluctuations of asthmatic children vary during a non-attack period, the rhythms changed to an ultradian rhythm (cycle length under 20 h) at the time of an asthma attack.

DISCUSSION

In the present study, we found that the rhythms in the 1/f fluctuations of HR of asthmatic children change to an ultradian rhythm during an asthma attack.

We were unable to calculate the rhythm of the 1/f fluctuations of HR in two subjects during the non-attack period and in one subject during an asthma attack. Because the MemCalc/Chiram cannot analyze rhythms with components less than 5 h, we consider that these subjects may have had rhythms with components less than 5 h. However, the most important reason is the fact that we cannot extract a specific rhythm of 1/f fluctuations of HR when rhythms calculated by MemCalc/Chiram have various cycle lengths. We could not observe any

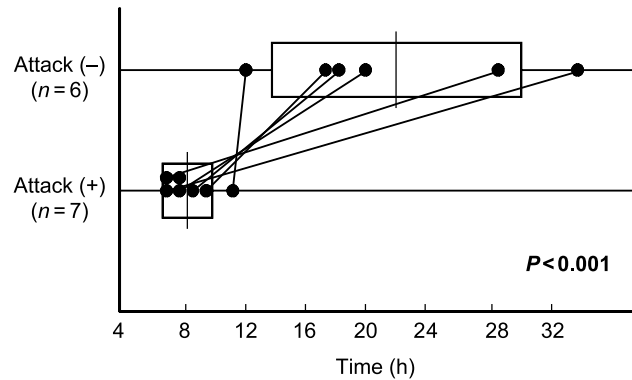


Fig. 3 Rhythms in 1/f fluctuations of heart rate (HR) for asthmatic children. Attack (-), non-attack period; attack (+), during an asthma attack.

difference in clinical profile between these three subjects (case 4, 5 and 7) and the other subjects in the study.

Although we compared the 1/f fluctuations of HR during an asthma attack and during a non-attack period in the same subjects, 24 h ECG for the non-attack period were recorded at home. In contrast, ECG recorded during an asthma attack were recorded at hospital. Because HRV is influenced by factors such as posture, eating, sleeping and smoking,⁹ our results do not necessarily show the real difference of 1/f fluctuations of HR during an asthma attack and during a non-attack period. However, in asthmatic children, the slope of the 1/f fluctuations of HR under a non-restricted state over a 24 h period was level on $\beta \neq 1$ (of $1/f^\beta$ fluctuations), similar to the slope in healthy children.

The presence of 1/f fluctuations of HR in a person shows the stability of internal parts of the body to varying environmental factors.¹⁰ When asthmatic children had an attack, they preserved the level of $\beta \neq 1$ on the $1/f^\beta$ fluctuations of HR for changing of internal parts of the body. For this method, we think that children having an asthma attack change the rhythm of 1/f fluctuations of HR from a circadian to an ultradian rhythm. In the present study, the median rhythm in asthmatic children during attack period was approximately 8 h, a so-called 'circaoctohoran rhythm'. In recent years, circaoctohoran rhythms have attracted attention in the field of chronobiology.¹¹ Li and Yorke¹² suggested 'period three implies chaos'. Because the circaoctohoran rhythm is 24 h divided into three equal parts, this rhythm is interesting as a point of tangency between biological rhythm and chaos. We think that biological rhythms in asthmatic children relate to some chaotic phenomena.

Herold *et al.*¹³ reported that plasma endothelin (ET)-1 is better characterized by a component of approximately 8 h than by a 24 h component. An association between asthma and ET-1 has been reported by some authors. Kraft *et al.*¹⁴ reported that ET-1 is higher in subjects with nocturnal asthma and plays a role in the overnight worsening of asthma. El-Gamal *et al.*¹⁵ reported that asthmatic children had higher ET-1 levels during asthma attacks than during quiescence of symptoms. It is interesting that asthmatic children during an asthma attack have a circaoctohoran rhythm of HR for keeping the level of $\beta \neq 1$ on the $1/f^\beta$ fluctuations at the time of an asthma attack although they have various rhythms of HR during a non-attack period. The circaoctohoran rhythm of asthmatic children may match the ET-1 rhythm during an acute attack. In future, we will examine the change in serum ET-1 levels at hourly intervals and describe the ET-1 rhythm in asthmatic children.

In conclusion, the present study demonstrates the difference in the rhythm of $1/f$ fluctuations over the ensuing 24 h in asthmatic children during an asthma attack and non-attack period. The clinical meaning of this rhythm of $1/f$ fluctuations in asthmatic children is unclear, but warrants examination.

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