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Nonlinearity Changes of 24 Hour Heart Rate Variability in Children with Tetralogy of Fallot

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활로씨 사징 수술 후 소아에서의 24시간 심박동의 비선형성 변화

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국문초록

연구배경 : 활로씨 사징(TOF) 수술 후 발생하는 심장 돌연사는 심실빈맥이 주 원인으로 인정되지만 아직 어떤 기전에 의해 돌연사가 발생하는지는 증명되지 않았다. 일부 심질환에서 심박동수의 변동과 심장 돌연사와의 관련성이 보고되고 있어 TOF 수술 후 심박동수의 변동에 대하여 알아보는 것이 심장 돌연사의 기전 규명에 도움이 될 것이다. 본 연구는 TOF 수술 후의 심박동수의 변동량을 측정하고 돌연사와의 관련성을 규명하기 위한 조사의 일환으로 시행되었다. **방 법** : TOF 수술을 받은 소아 중에서 증상이 없고 유의한 혈역학 장애와 심실 부정맥이 없는 소아 집단(남아 10명, 여아 3명 ; 평균 연령, 9년 3개월 ; 평균 수술 후 기간, 7년)을 대상으로 24시간 심전도에서의 심박동의 복잡하고 주기적인 동역학을 구하여 정상 소아 대조군(평균 연령 8년 10개월)과 비교하였다. 각각의 소아에서의 24시간 홀터 심전도를 각각 1시간 길이로 나누어 각각의 심박동 시계열 데이터에 대하여 correlation dimension을 이용하여 전체적인 복잡성을 정량화 하였으며, 파워 스펙트럼을 구하여 저주파성분(0.08 0.15 Hz)과 고주파성분(0.15 0.4 Hz)을 계산한 후, 각 집단간의 결과들을 비교하였다. **결 과** : TOF 집단이 대조군보다 더 낮은 correlation dimension(4.055±0.4134 vs. 4.9310±0.2054, $p<0.05$)을 가졌다. 그러나 파워 스펙트럼의 저주파성분(0.9864±0.5598 vs. 1.5560±0.8325, $p<0.05$)과 고주파성분(1.1168±0.1.1448 vs. 0.9271±0.6528, $p<0.05$)의 조사에서는 두 집단간의 유의한 차이가 발생하지 않았다. **결 론** : TOF 수술 후 집단의 심박동 시계열 데이터가 정상 소아 집단의 경우에 비해 더 규칙적이었다. 이런 현상은 파워 스펙트럼상에서는 유의하게 나타나지 않았고 correlation dimension을 이용하여 심박동 시계열 데이터의 비선형 특성을 밝힐 수 있었다. TOF 수술 후 집단에서의 규칙적인 심박동 시계열 데이터의 의미는 현재로는 불확실 하지만 이 군에서의 심장 돌연사와의 관련성을 암시할 수 있는 현상으로 추정된다. **(Korean Circulation J 1998;28(5):774-780)**

중심 단어 : 심박성 변동량 · 24시간 홀터 심전도 · 상관차원 · 활로씨 사징.

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Introduction

Heart rate variability (HRV) has been studied in many conditions because it allows non-invasive evaluation of the state of autonomic nervous system. It has been demonstrated that HRV has two major spectral components : high frequency (HF) component (0.15 - 0.35 Hz) and low frequency (LF) component (0.05 - 0.15 Hz).[1] HF component is associated with the respiratory cycle and is mostly mediated by vagal cardiac control. Although the origins of LF component are less well established, they seem to be associated with baroreceptor reflex control and thermoregulatory system and controlled by both sympathetic and parasympathetic nervous systems. The HF/LF ratio is a useful parameter to quantify sympatho-vagal balance in cardiac automatic control. Three kinds of methods are suggested to quantify HRV : time-domain analysis, frequency domain analysis, and nonlinear dynamics analysis. Because of the close correlation between time-domain analysis and frequency-domain analysis and being easier to interpret and apply frequeency-domain analysis to the physiological meaning compared to time-domain analysis, the frequency-domain analysis is preferred.

Recently it has been studied widely whether HRV has nonlinear characteristics or not. To detect nonlinearity or local characteristics of the biological signals that are not detected by the conventional frequency domain analysis, new methods such as nonlinear dynamics theory, bispectrum, wavelet trans-form, time-frequency domain analysis, are suggested. In this investigation we adopted correlation dimension that were most widely used in the nonlinear dynamics theory to quantify the nonlinearity of HRV. There are many clinical reports on the decrease of correlation dimension, that is decrease of nonlinearity, of HRV in adults with lethal cardiac arrhythmia,[2] in aging,[3] in newborn babies with sudden infant death syndrome,[4] and in sick newborn babies.[3]

This study was aimed to evaluate whether alteration of the heart rate dynamics occur in postoperative TOF by analyzing the changes of heart rate dynamics by means of correlation dimension analysis and frequency domain analysis.

Materials and Methods

Among the children who had been followed up in the outpatient clinic of Seoul National University Children's Hospital, we acquired 24-hour Holter ECG data of 13 asymptomatic children after operation of tetralogy of Fallot (10 boys, 3 girls ; mean age, 9 years 3 months, range 5 years 11 months 14 years ; mean duration after operation, 7 years, range 4 years 10 years) and 13 age-matched normal children (mean age 8 years 10 months, range 6 years 13 years). The study group was selected among postoperative TOF children according to the following criteria: age at the time of study between 5 to 15 years old ; asymptomatic and in good hemodynamic status (Doppler velocity of tricuspid regurgitation 2.5 m/sec and mild pulmonary regurgitation) ; no ventricular arrhythmia. We acquired the raw ECG data from 24-hour Holter system (Delmar 9000A, USA) and recorded the digitized ECG in the personal computer using A/D converter (DT3000, Data Translation). To acquire 24-hour ECG data efficiently, we speeded up the reading speed of the Holter system 120 times as fast as normal writing speed, and sampled the ECG data at 60KHz. In effect, the effective sampling rate was 500Hz and it took about 15 minutes to acquire a 24-hour ECG data.

To improve the R-peak detection on Holter ECG that had much more noise and fluctuation than resting ECG, we modified Tompkins' algorithm to detect R-peak and determined RR interval as the intervals between successive R peak values. To estimate correct power spectral density function, we made RR interval data equi-time interval as Berger et al suggested.[5] Since the power spectrum of RR intervals was mainly concentrated below 1 Hz, Nyquist sampling rate was about 2 Hz. We sampled RR interval data at 4 Hz to eliminate the distortion that might arise in the high frequency region. We detrended the interpolated RR interval data to eliminate DC component, and applied Welch's averaged periodgram method to estimate power spectral density function. In this algorithm, we used hanning window using 1024 data points as the window. We normalized the power spectrum to compare the results between data and determined high frequency (HF) component (0.15 - 0.4 Hz), low frequency (LF) component (0.08 - 0.15 H) and the HF/LF power ratio. Although Grassberger and Procaccia suggested a correlation dimension that measured the nonlinearity of the time series data and estimated it by a procedure based on nearest-neighbors' distances,[6] we adopted Takens ML (maximum likelihood) estimator of correl-ation dimension in this study.[7]

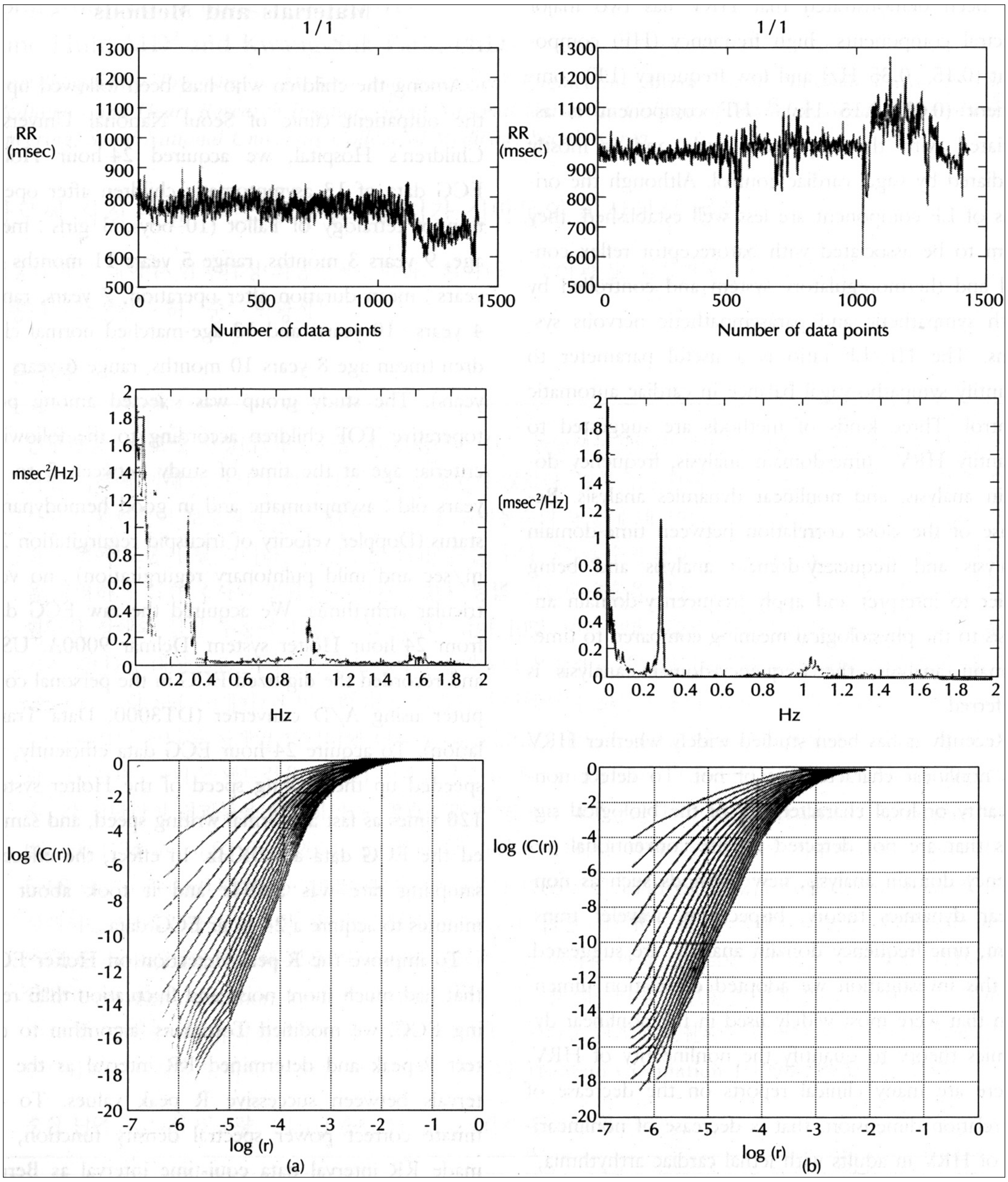

Fig. 1. HRV time series (top), power spectrum (middle), and correlation interal (bottom) of TOF group (a) and normal group (b). Note that in the bottom figures the curve which corresponds to embedding dimension 3 is the most left-side, and the curve which corresponds to embedding dimension 3 is the most left-side, and the curve which corresponds to embedding dimension 20 is the most right-side.

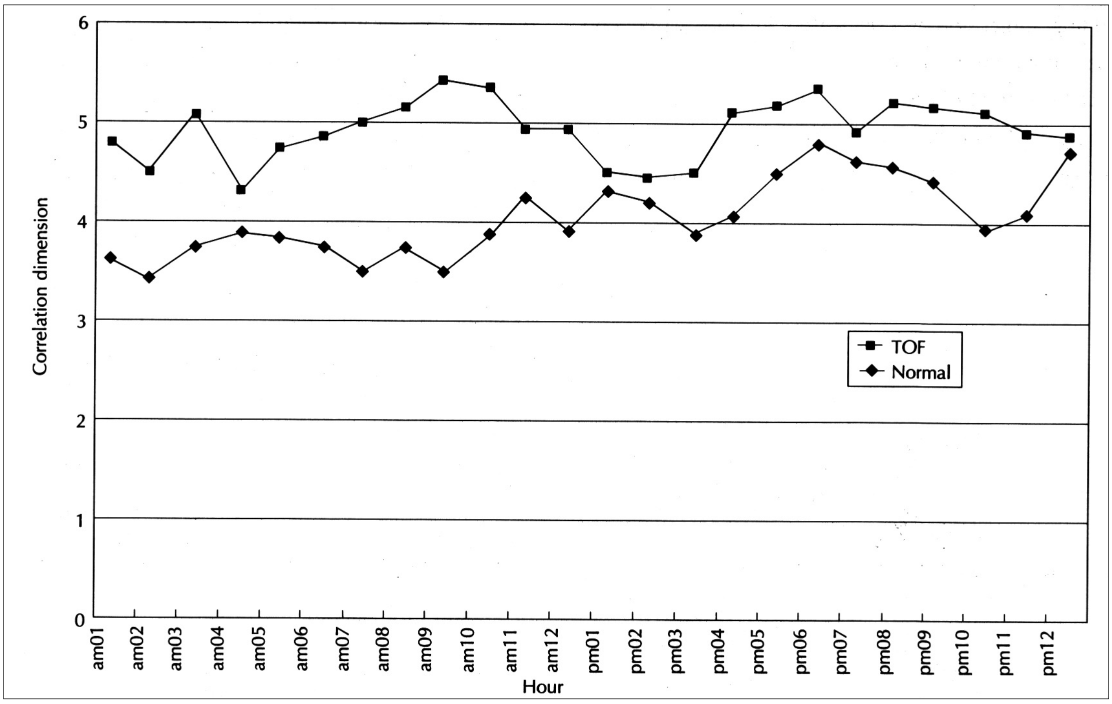

Fig. 2. The mean of correlation dimnsion each hour throughout 24 hours from TOF and normal group.

$$C\ (r) = \Pr\{D_{mm} < r\} = ar^{p}\ \{1 + br^{r} + O\ (r^{r})\}$$

Ï ar^{p}, $r < \varepsilon$

$$\tilde{p} = MI\ \sum_{j=}^{M} \log\ (\varepsilon / D_j)$$

Where C (r) is the correlation integral, and $\tilde{p}$ is the Takens maximum likelihood estimator for some small known.

By calculating the first zero crossing point on the autocorrelation function curve of HRV, we decided 3 times of the value as the window length for one vector (=time delay *embedding dimension). In this study we fixed the embedding dimension as 10 and calculated the proper time delay to determine the correlation dimension.

To test the statistical difference of mean, variance, HF, LF, HF/LF and correlation dimension between normal and TOF group, we used student t test assuming equal or unequal variances. First, we determined the difference throughout 24 hours, and the difference of each hour period. All the analyses were performed using 0.05 as the criterion for statistical significance. All the data are presented as mean value standard deviation.

Results

Fig. 1 represents the time series plot of RR interval, power spectrum and correlation of the TOF group and normal group at a time period between 1 A.M. and 2 A.M.. We did not find any difference between two groups either in the time series plot or in the power spectrum. In the power spectrum, LF and HF components were clearly seen in both groups. The bottom figures represent the change of the correlation integrals as the embedding dimension increases from 3 to 20. In the correlation integral graph, the correlation dimension, that is, the slope of the correlation integral, was saturated as the embedding dimension was increased in both cases, and the saturation value of normal case (b) was higher than that of TOF case (a).

Fig. 2 shows that the mean of the correlation dimension of the normal group was always higher than that of the TOF group at each hour length throughout 24 hours, and the difference was statistically significant. It was verified by the student t test for 1-hour length HRV and for 24-hour length HRV using 0.05 as a significant level and assuming an equal or non-equal variances. The mean of total 24-hour HRV of correlation dimension was also significantly higher in the normal group than in the TOF group (Fig. 3).

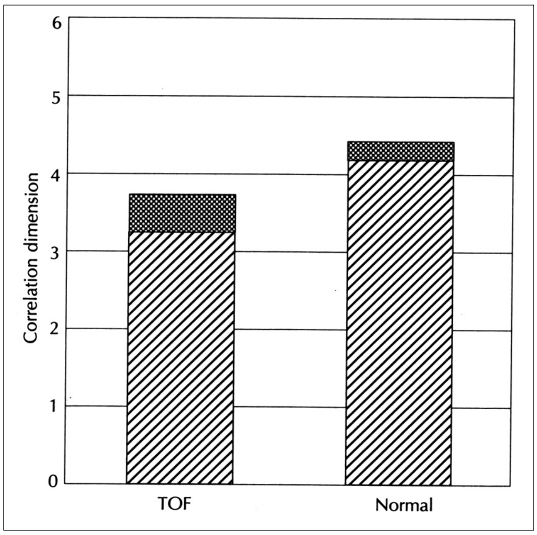

Fig. 3. Comparison of the mean and standard deviation of 24-hour HRV between TOF nd normal group.

Although the power spectrum has been widely used to detect abnormal conditions, LF and HF components showed no significant difference between two groups in this study (Figs. 4 and 5). It was also noted that LF and HF components were higher in the nighttime than in the daytime, while correlation dimension was almost constant both in the nighttime and in the daytime.

Discussion

In some children with postoperative TOF, ventricular arrhythmia and/or sudden cardiac death may occur. This catastrophic event of sudden cardiac death is believed to be related to sustained ventricular tachycardia or ventricular fibrillation. However, the connecting mechanism between clinical findings and sustained ventricular arrhythmia and/or sudden cardiac death is not defined yet.[8) This study was performed based on the idea that these episodes after TOF operation might be related to the alterations of the environment surrounding the heart. This is based on our recent experience of two cases that developed sustained ventricular tachycardia one year after

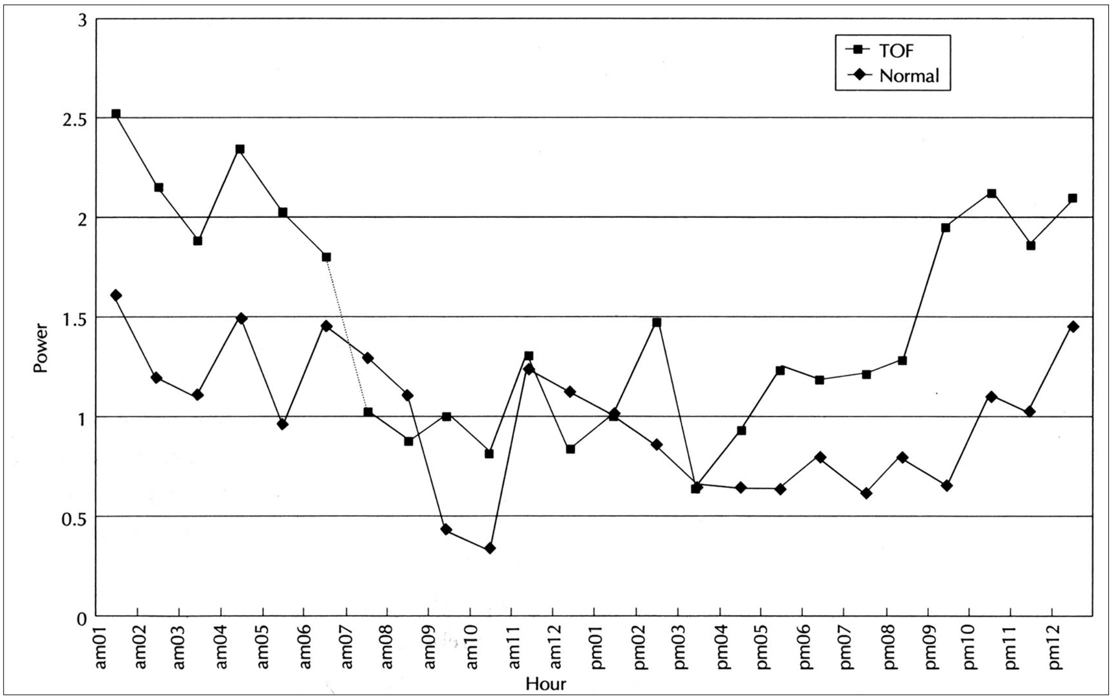

Fig. 4. Comparison of the mean of LF (0.05 - 0.15 Hz) component each hour throughout 24 hours between TOF and normal group.

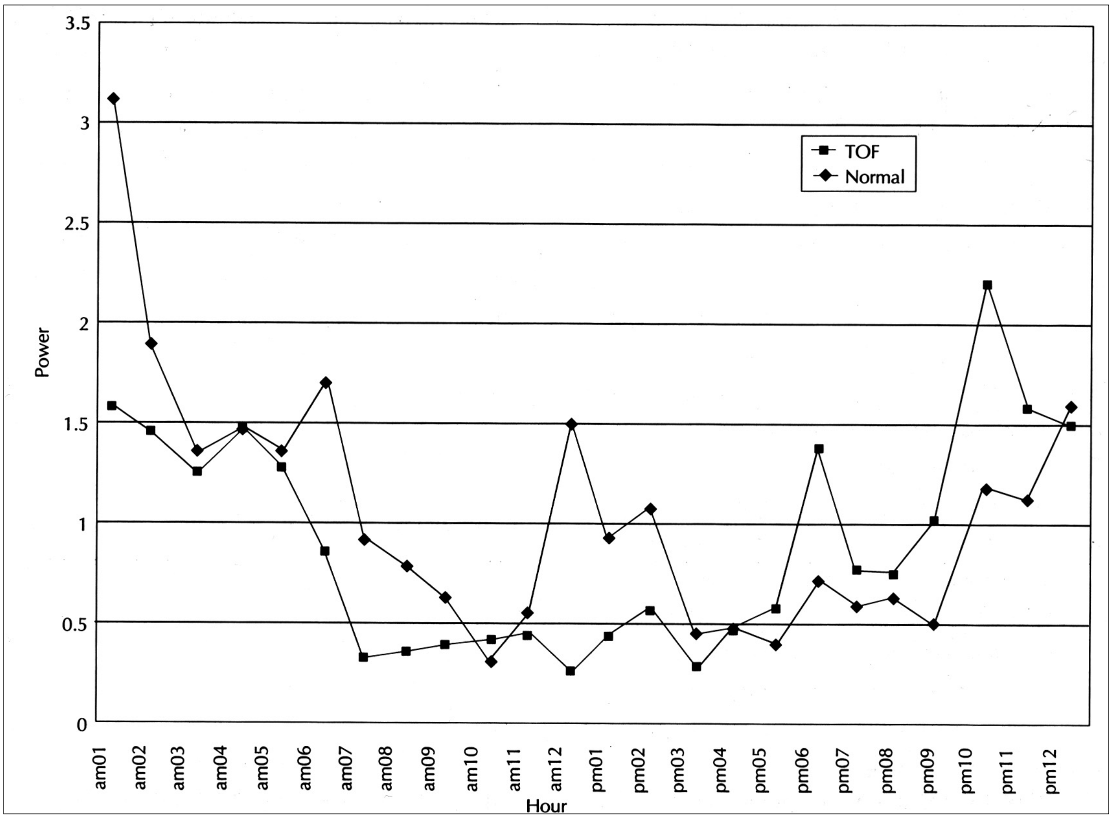

Fig. 5. Comparison of the mean of HF (0.15 - 0.35 Hz) component each hour throughout 24 hours between TOF and normal group.

correction of TOF. Both of them were asymptomatic and were in good hemodynamic status besides moderate pulmonary regurgitation. Sustained ventricular tachycardia, which had continued for several hours were terminated by cardioversion. The implication of these cases was that additional factor is necessary for the ventricular tachycardia to degenerate into ventricular fibrillation. We suspect that sympathovagal imbalance is one of the culprits for the development of ventricular fibrillation and sudden cardiac death after operation for tetralogy of Fallot. Because sympathovagal imbalance can be assessed by analyzing the heart rate dynamics, we intended to verify this hypothesis by measuring the heart rate variability.

In this study, although the change in heart rate variation was not statistically verified by the conventional HRV analysis such as power spectral analysis, nonlinear dynamics analysis by means of correlation dimension reflected the effect. In general, power spectral density analysis method quantifies how and which periodic are dominant components of the time series data. Considering the fact that cardiac activities show nonlinear characteristics, it is not possible to reveal the entire characteristics of heart rate dynamics by using only linear methods such as power spectral density analysis. This is the reason why another method such as correlation dimension is needed to quantify the nonlinear characteristics of heart rate dynamics. But, as the differences between different hours are clearly shown in the power spectral density analysis, it is necessary to perform both power spectral density analysis and correlation dimension to reveal the exact nature of heart rate dynamics.

Our preliminary study showed that TOF children had a lower correlation dimension than normal children. It can be inferred from this observations that lower correlation dimension may be one of the contributory factors to sudden cardiac death after TOF operation.

This assumption is not contradictory to the previous studies reporting that diseased population has lower correlation dimension than normal population.[2-4) However, because previous studies were mostly done on patients without cardiac surgery and without congenital heart disease, simple assumption based on the previous reports may not be applicable in this study.

There are several limitations in this study. Firstly, we did not evaluate the change of heart rate among children with complex ventricular arrhythmias for the lack of the materials. Because complex ventricular tachycardia in these children is regarded as a major factor to sudden death,[8) it is necessary to define the heart rate dynamics in children with complex ventricular arrhyhtmias. However, it may be difficult to acquire enough heart rate data that is not affected by the ventricular arrhythmias. Secondly, there is a possibility that changes in heart rate dynamics may not be specific to these postoperative TOF children. Because of the possible damage of nerve innervations and/or blood supply to the sinus node, changes in heart rate dynamics could occur after cardiac operation of various cardiac defects. Further evaluation of heart rate dynamics in children with other types of cardiac defect or ventricular arrhythmia or longitudinal study from the preoperative state can help to solve these problems.

Acknowledging these limitations, we conclude that even in children who are apparently in good postoperative state, electrophysiological environment differs from that of normal children and that correlation dimension is a useful method in the study of heart rate dynamics. In addition to the conventional method of power spectral analysis, we consider nonlinear dynamics analysis necessary in the evaluation of heart rate dynamics. Because we can not interpret clearly the physiological meaning of these results, we think that further experiments and studies are necessary to understand the meaning of nonlinear characteristics of cardiac activities in this group of children.

KEY WORDS：Heart rate variability · 24-hour Holter ECT · Correlation dimension · Power spectral analysis · Tetralogy of fallot..

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