Change of Complex and Periodic Heart Rate Dynamics with Change of Pulmonary Artery Pressure in Infants with Ventricular Septal Defect*

Myung Kul Yum, M.D., Nam Su Kim, M.D., Hyang Ok Woo, M.D.**

Department of Pediatric Cardiology, School of Medicine, Hanyang University, Seoul, Korea
*Department of Pediatric Cardiology,** College of Medicine, Gyeongsang National University, Chinju, Korea*

심실중격결손을 가진 영유아에서 폐동맥 압력의 변화와 복잡 및 주기적 심박동수 동력성과의 관계

한양대학교 의과대학 소아과학교실, 경상대학교 의과대학 소아과학교실**
염명걸 · 김남수 · 우향옥**

= 국문초록 =

연구배경 : 폐동맥 압력의 변화와 주기성과 복잡성을 가진 심박동수 동력성과의 상관관계를 알아보고, 이러한 심박동수 동력의 변이성으로 평균 폐동맥 압력을 비침습적인 방법으로 예견이 가능한지 알아보고자 본 연구를 시행하였다.

방 법 : 심실중격결손을 가진 32명의 영유아를 대상으로 심도자술을 시행하는 동안 평균 폐동맥 압력을 계속 측정하면서 동시에 5분 이상 심전도를 감시하고 자료를 수집하였다. 또한, 고주파수(>0.15Hz)와 저주파수(0.03 -0.15Hz)를 보이는 심박동수 변이성을 스펙트럴 분석(spectral analysis)을 이용해 계산하고 전체 심박동 시간의 일련의 복잡성을 근사 엔트로피(approximate entropy)에 의해 정량화하였다.

결 과 : 평균 폐동맥압이 20mmHg 이상인 폐동맥 고혈압 영유아가 평균 폐동맥압이 20mmHg 이하인 정상 폐동맥압 영유아보다 저주파수와 고주파수의 심박동수 변이성이 의미있게 낮게 나왔으며, 심박동수 동력성의 복잡성을 나타내는 근사 엔트로피도 의미있게 낮았다. 평균 폐동맥 압력은 심박동수 변이성의 크기인 스펙트럴 파워(spectral powers)보다는 심박동수 변이성의 근사 엔트로피와 의미있는 상관관계를 보였다.

결 론 : 좌우 단락으로 인한 폐동맥 고혈압증을 가진 영유아에서는 주기적이고 복잡성을 가진 심박동수의 진동이 억제되고 있음을 알 수 있고, 심박동수 변이성의 근사 엔트로피를 이용하여 비침습적인 방법으로 평균 폐동맥 압력을 예측할 수 있음을 알 수 있었다.

중심 단어 : Pulmonary hypertension Heart rate complexity Approximate entropy.

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Introduction

One of the most difficult challenges facing pediatric cardiologists in managing infants with left-to-right shunt lesion is to estimate and treat pulmonary hypertension. It derives from an increase in flow, a direct transmission of systemic pressure to the pulmonary artery, and an increase in pulmonary vascular resistance. It impairs optimizing hydraulic power output of right ventricle[1,2]. The resultant pressure and volume overload of the right ventricle leftward shifts the interventricular septum and compromise systolic function and diastolic compliance of the left ventricle[3]. The pulmonary hypertension induced by left-to-right shunt lesion, therefore, alters the homeostasis of pulmonary and systemic circulation. This may result in perturbation of heart rate control systems, such as respiratory modulatory[4], autonomic nervous[5] and baroreceptor reflexes systems[6] and may result in the emergence of different behavior in heart rate. The power spectral analysis and recently described measures derived from nonlinear dynamics provide information about the dynamics of heart rate and the underlying heart rate control sysems[7-10]. Especially, approximate entropy of heart rate has been known to provide an index to quantify the degree of perturbation of the nonlinear dynamic process by quantifying the complexity of heart rate fluctuation[11,12]. However, there has been no study about the integrated dynamics of heart rate and its control system in infants with pulmonary hypertension due to left-to-right shunt.

Motivated by this, we hypothesize that in infants with left-to-right shunt, the heart rate generating processes are perturbed progressively as pulmonary artery pressure elevates and this will alter the heart rate dynamics in a linear or nonlinear manner. We propose to test this hypothesis by determining whether the spectral power and approximate entropy of heart rate variability decrease as pulmonary artery pressure elevates. This relationship may provide another noninvasive means to estimate pulmonary artery pressure in infants with left-to-right shunt lesion.

Subjects and Methods

Our subjects were thirty two infants, aged less than twelve months with ventricular septal defect. Informed consent was obtained and the study was approved by the Committee on Human Experimentation of Hanyang University. No infants had other associated cardiac anomalies or myocardial dysfunction. The patients were divided into two groups : pulmonary *normotensive* (mean pulmonary artery pressure $\leq$20mmHg, n=15) and pulmonary *hypertensive* (mean pulmonary artery pressure >20mmHg, n=17). Cardiac catheterization was underwent between 10 a.m. and midday after 3mg/kg of ketamine was given intramuscularly and simultanesous intravenous ketamine 1mg/kg was given intravenously. After catheter entered the left pulmonary artery, another ketamine of 1mg/kg was given intravenously and signals of mean left pulmonary artery pressure and electrocardiogram were simultaneously monitored for more than five minutes. Analog signals of monitored electrocardiogram were stored on a videotape via pulse code modulator (Sony PCM-501 ES digital audio processor) and a videocassette recorder (Samsung SV-899). If gross body movement was found, we restarted recording so that recorded electrocardiogram would not be affected by gross body movement. After the recording, other hemodynamic measurements were completed. The analog signals of electrocardiogram which were replayed by the pulse code modulator and the videocassette recorder were sampled with an analog-to-digital conversion (PCL-718 analog-to-digital converter, Taiwan) with the rate of 1000 hertz and then stored on binary files. From this electrocardiographic data, five-minute sections free of ectopic beats or artifacts were selected. RR intervals were measured, 1000 hertz linearly interpolated by its RR interval to construct a real time series of RR intervals, and 4 hertz subsampled. We extracted

256-seconds(x 4 hertz=1024 points) time series of RR intervals.

Power spectral density function was estimated by conventional methods. We calculated low-and high-frequency power by integrating the power spectral density curve at 0.03 - 0.15Hz range and the above 0.15 Hz range[13-15]. The high/low frequency power ratio was also calculated.

The methodological details for computing approximate entropy, ApEn(m,r,N), have been published elsewhere[11,12,16]. In order to compute ApEn(m,r,N), three input parameters should be fixed : m is the length of compared runs, and r is the effective filter. N is the length of data points. In brief, it measures the logarithmic conditional probability which is, given that m successive heart beats are close(within the range of r) to certain m successive template beats, the probability of $m+1$ beat are close(within the range of r) to the template $m+1$ heart beat. Let each heart rate data set be represented as $u(i)$. From the $u(i)$, form vector sequences $x(1)$ through $x(N-m+1)$, defined by $x(i)=[u(i),...,u(i+m-1)]$. These vectors represent m consecutive u values, commencing with the ith point. Define the distance d[$x(i)$, $x(j)$] between vector $x(i)$ and $x(j)$ as the maximum difference in their respective scalar components. Use the sequence $x(1)$, $x(2)$,...., $x(N-m+1)$ to construct, for each $i \leq N-m+1$, $c_i^m(r)=$ (*numbers of* $j \leq N-m+1$ such that d[$x(i)$, $x(j)$]$\leq r$)/$(N-m+1)$. Define $\Phi^m(r)=(N-m+1)^{-1}\sum_i=1^{N-m+1}\ \mathrm{lnc}_i^m(r)$, where ln is the natural loga-rithm, and then define the parameter ApEn(m,r,N) = $\Phi^{m+1}(r)$ - $\Phi^m(r)$. For this study $N=1024$ points (256 seconds) and two parameters are that $m=2$ and $r=20\%$ standard deviation of each data set. These values were selected on the basis of previous studies indicating good statistical validity for approximate entropy within these variable ranges[17-20].

All data are presented as mean values±1 standard deviation. Differences in logarithmic low-and high-frequency power, high/low frequency power ratio, and approximate entropy from pulmonary *hypertensive* to pulmonary *normotensive* infants were analyzed by means of unpaired t tests. Linear regression was used to examine the relation between the mean pulmonary artery pressure and the logarithmic low- and high-frequency power and the approximate entropy. Data were analyzed using SAS(V6.02). All analyses were performed using an alpha level of 0.05 as a criterion for statistical sig-

Table 1. Clinical Characteristics, Spectral Power, and Approximate Entropy

	Mean pulmonary artery pressure ≤20mmHg (n=15)	Mean pulmonary artery pressure >20mmHg (n=17)	p
Age(months)	10.8 ± 2.1 (8 - 12)	5.2 ± 2.8 (2 - 9)	<0.001
Mean pulmonary artery pressure(mmHg)	14.3 ± 2.3	33.3 ± 9.8	<0.001
Qp/Qs	1.63± 0.73	2.76 ± 1.38	<0.05
Rp/Rs	0.14± 0.06	0.22 ± 0.09	<0.05
RR interval			
Mean(msec)	610 ±92	532 ±107	NS
Standard deviation(msec²)	40.1 ±59.1	25.1 ± 32.3	NS
Logarithmic spectral power(msec²)			
Low-frequency power(0.03 - 0.15 Hz)	2.14± 0.66	1.02 ± 1.03	<0.05
High-frequency power(0.15 - 1 Hz)	2.13± 0.50	1.44 ± 0.85	<0.05
High/low frequency power ratio	1.61± 1.21	3.08 ± 3.07	NS
Heart rate complexity(Approximate entropy)	0.827±0.108	0.624± 0.124	<0.001

values are mean±S.D.
NS : not significant

nificance.

Results

Comparisons of clinical characteristics, spectral power and approximate entropy between pulmonary *hypertensive* and *normotensive* infants are summarized in Table 1.

1. Clinical characteristics

There were no differences in basal mean heart rate (RR interval) and heart rate variability measured as standard deviation of heart rate between the two groups.

2. Frequency domain heart rate statistic

The low- and high-frequency power of the heart rate were significantly lower in pulmonary *hypertensive* than in *normotensive* infants ($p<0.05$). The high/low

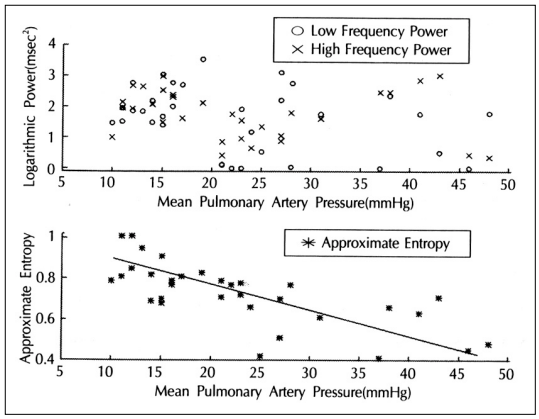

Fig. 1. Top : Effect of mean pulmonary artery pressure on logarithmic low-and high-frequency power. There were no significant linear correlations between them (R^2=0.11, p=0.06 and R^2=0.04, p=0.29, respectively). Bottom : Effect of mean pulmonary artery pressure on heart rate complexity(approximate entropy). There is a significant negative linear correlation between the approximate entropy and mean pulmonary artery pressure (R^2= - 0.51, p=0.0001).

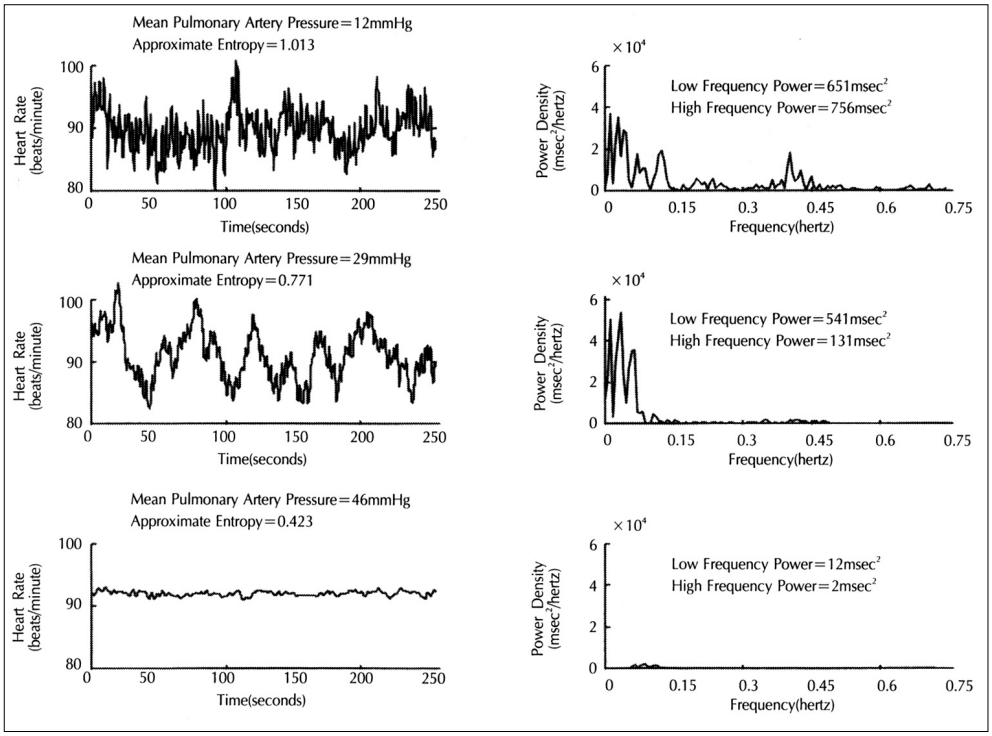

Fig. 2. Heart rate-time series with approximate entropy(left hand column) and their corresponding power spectral density functions with low- and high-frequency power(right hand column) in three infants with different mean pulmonary artery pressure of 12mmHg(top), 29mmHg(middle), and 46mmHg(bottom), respectively. Note decline of the beat-to-beat complexity in heart rate tracings and their corresponding approximate entropy of heart rate as pulmonary artery pressure elevates. The spectral powers are markedly decreased in infants with high pulmonary artery pressure(bottom), however, their decline were not in linear manner with the elevation of the pulmonary artery pressure. See also Fig. 1.

frequency power ratio was not significantly different. There was no significant correlation between the logarithmic low-($R^2=0.11$, $p=0.06$) and high-($R^2=0.04$, $p=0.29$) frequency power and mean pulmonary artery pressure(Fig. 1, top).

3. Heart rate complexity statistic

There was a significant difference in the approximate entropy value in the two groups($p<0.001$). In other words, the complexity of heart rate dynamics was significantly decreased in pulmonary *hypertensive* infants. Fig. 2 illustrates three representative examples of heart rate-time series of 256 seconds(left hand column) and its power spectra(right hand column) obtained in three infants with different mean pulmonary artery pressure of 12mmHg, 29mmHg, and 42mmHg, respectively. Note completely different heart rate dynamic in time and frequency domain between these infants：In one infant with normal mean pulmonary artery pressure of 12mmHg(Fig. 2, top), there is evident beat-to-beat heart rate complexity resulting in high approximate entropy of 1.013. The significant low- frequency and high-frequency oscillation contributes to this high irregularity. In another infant with slightly elevated mean pulmonary artery pressure of 29mmHg(Fig. 2, middle), despite the significant low-frequency oscillation, the approximate entropy of 0.771 is lower than that of the previous infant. The significant decrease in high-frequency power may contribute to the decrease of irregularity. In the other infant with significantly elevated mean pulmonary artery pressure of 46mmHg(Fig. 2, bottom), the heart rate tracing shows very little beat-to-beat fluctuations. It resembles a sinusoidal wave of low amplitude. Its approximate entropy value is 0.423. The markedly decreased high- and low-frequency power contributes to this decrease of irregularity. This dependence of approximate entropy on pulmonary artery pressure was further confirmed by correlation analysis, which showed significant negative correlation between pulmonary artery pressure and approximate entropy values(Fig. 1, bottom). The relationship is mean pulmonary artery pressure$=-51.47\times$(approximate entropy)$+60.28$, ($R^2=-0.51$, $p=0.0001$).

Discussion

The major new observations of this investigation are that, in infants suffering from pulmonary hypertension due to left-to-right shunt lesions, the high- and low-frequency oscillation and the overall complexity of heart rate dynamics are clearly suppressed. Furthermore, the suppression of the complexity, unlike spectral power, linearly correlated with the elevation of pulmonary artery pressure. Therefore in infants with extremely high pulmonary artery pressure, the tracing of heart rate appeared like a sinusoid or straight line. These results indicate that the pulmonary artery pressure may be one of the determinant of heart rate complexity and cardiovascular sickness, and quantifying beat-to-beat heart rate complexity using approximate entropy may provide a new way of noninvasively estimating mean pulmonary artery pressure in infants with left-to-right shunt lesions.

1. Effects of pulmonary hypertension on mean basal heart rate and standard deviation of heart rate

Pulmonary hypertension did not significantly affect the mean basal heart rate and standard deviation. Because the conventional first and second order moment statistics do not take into account beat to beat dynamic of heart rate fluctuation[19], they can not reflect the altered physiological status, such as pulmonary hypertension.

2. Effects of pulmonary hypertension on frequency domain heart rate variability

In *normotensive* infants, both low- and high-frequency oscillations are clearly seen in most cases(Fig. 2, top), which implies that heart rate is well modulated by the autonomic nervous system, as in normal, healthy adults[20,21]. In the pulmonary *hypertensive* infants,

on the contrary, the low- and/or high- frequency oscillation significantly decreased(Fig. 2, middle and bottom), which means that autonomic control of heart rate is significantly blunted in pulmonary *hypertensive* infants. It has been documented, in adults, that high-frequency oscillations are attenuated with congestive heart failure[5], aging[22], and coronary heart disease[23,24]. The decline of high- frequency oscillation in pulmonary *hypertensive* infants is to be related to their higher respiration rate[3,20], which is known to decrease the respiratory sinus arrhythmia, and is likely to be related to decreased heart rate response to direct vagal stimulation, which is seen in congestive heart failure[25]. It was also documented that low-frequency oscillation was decreased in chronic congestive heart failure due to abnormalities at the baroreceptor[5,6,25], adrenoreceptor, and subreceptor level[26]. These abnormalities may play a role in decreasing the low-frequency oscillation in our pulmonary *hypertensive* infants. Although elevation of pulmonary artery pressure significantly lowers the two oscillation, it does not do this in a linear manner.

3. Effects of pulmonary hypertension on complexity of heart rate variability

The fact that mean pulmonary artery pressure was inversely correlated with approximate entropy indicates that increase in pulmonary artery pressure proportionally suppresses the complexity of heart rate variability. So the plot of heart rate evolves from irregular to regular shape such as sinusoidal or linear shape(Fig. 2, left hand column). It has been widely accepted that the complexity of heart rate reflects cardiovascular health[7-10,27]. Therefore, the physiologic meaning of the above inverse correlation is that, in infants with left-to-right shunt lesions, increasing pulmonary artery pressure deteriorates overall cardiovascular health in a linear manner. As pulmonary artery pressure increases, infants lose the complexity of heart rate variability, which makes the infants less pliable and more vulnerable to internal or external cardiovascular stress. Furthermore, unlike the spectral indexes, this inverse correlation enables us to predict the mean pulmonary artery pressure by calculating approximate entropy. Heart rate variability is determined by the underlying heart rate generating process, which is, in turn, determined by the status of underlying heart rate control system[8,10]. If the heart rate control systems are multiple and are coupled tightly to each other, which is the hallmark of a healthy cardiovascular system, the heart rate generating process becomes nonlinear[28,29] and/or stochastic[10]. The generated heart rate, therefore, tends to overshoot or undershoot(nonlinear) and/or to change in a random direction(inease or decrease : stochastic). So the beat-to-beat heart rate changes can not be predicted and the overall heart rate becomes very complex and irregular. On the contrary, if there are not multiple heart rate control systems or if they are not tightly coupled to each other, which emerges in a sick cardiovascular system, the heart rate generating process become linear and determinstic. As a result, the generated heart rate is linear or periodic and the heart rate fluctuation becomes predictable and simple, and the overall complexity is lost[8,10,28-30]. Pulmonary hypertension, due to increased pulmonary blood flow in infants, produces not only systolic and diastolic dysfunction of both ventricles but also impairs lung mechanic, such as decline of lung compliance[31], all of which affects the heart rate control system[3-5]. These alterations in heart rate regulating systems are followed by disruption of tight coupling between them, which shift the heart rate generating process from nonlinear and/or stochastic to linear, and finally make the heart rate variability less complex. There are two limitations of this study. One is unavoidable use of ketamine to sedate the infants. Ketamine elevates systemic artery pressure, which in turn may affect heart rate variability of both groups. Therefore, we cannot exclude with certainty the possibility that difference of heart rate variability between two groups may originate from the variable response of blood pressure to ketamine. The other is mean age difference between the two groups was about five months. It is unlikely, however, that the age difference of five mon-

ths affected the heart rate variability during the state of sedation.

In infants, it is very difficult to quantitatively estimate cardiovascular status by noninvasive and even by invasive means. As we documented hitherto, the quantitative nonlinear measure of heart rate variability such as approximate entropy, appears to be a new promising tool for monitoring cardiovascular status, such as pulmonary artery presssure.

Summary

1. Background

We studied how periodic and complex heart rate dynamic changes as pulmonary artery pressure increases in 32 infants with ventricular septal defect. In addition, we tested the possibility that the dynamical changes can be used to noninvasively predict the pulmonary artery pressure.

2. Methods

During cardiac catheterization, mean pulmonary artery pressure was measured and, at the same time, 5-minute segments of continuos electrocardiographic recording was stored. High-(>0.15 hertz) and low-(0.03 - 0.15 hertz) frequency components of heart rate variability were computed using spectral analysis. The overall complexity of heart rate time series was quantified by its approximate entropy.

3. Results

Pulmonary *hypertensive* infants (mean pulmonary artery pressure >20mmHg, n=17) had significantly lower low-($p<0.05$) and high-($p<0.05$) frequency power and lower approximate entropy($p<0.0001$) than pulmonary *normotensive* infants(mean pulmonary artery pressure ≤20mmHg, n=15). The mean pul-monary artery pressure was significantly correlated not with the spectral powers but with the approximate entropy ($R^2 = -0.51$, $p=0.0001$).

4. Conclusion

It can be concluded that, in infants, pulmonary hypertension induced by left-to-right shunt lesions suppress both periodic and complex heart rate oscillation and that mean pulmonary artery pressure can be predicted by calculating approximate entropy of heart rate variability.

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