Analysis of Cardiovascular Time Series using Multivariate Sample Entropy: A Comparison between Normal and Congestive Heart Failure Subjects

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Abstract

The cardiovascular (CV) system typically exhibits complex dynamical behavior, which is reflected not only within a single data channel, but more importantly across data channels. Multivariate sample entropy (MSE) has been proven as a useful tool to analyze both the within- and cross-channel coupled dynamics, providing an insight into the underlying system complexity and coupling relationship. In this study, the MSE method was used to monitor both the univariate and multivariate CV time series variability, focusing on identifying the differences between normal and congestive heart failure (CHF) subjects. Electrocardiogram, phonocardiogram and radial artery pressure waveforms were simultaneously recorded from 30 normal and 30 CHF subjects to determine three CV time series: RR interval, cardiac systolic time interval (STI) and pulse transit time (PTT). The MSE method was applied to univariate (RR, STI, PTT), bivariate (RR & STI, RR & PTT, STI & PTT) and trivariate (RR & STI & PTT) time series. The results showed that all MSE values in the CHF group were significantly lower than for the normal group (all $P<0.05$, except for the univariate PTT series), which indicates that the complexity of univariate series decreased and the synchronization of multivariate series increased for CHF subjects. Moreover, the statistical significance between the two subject groups increased from using univariate to multivariate time series (with $P<0.05$ to $P<0.001$), confirming the advantage of multivariate analysis.

1. Introduction

Short-term, beat-to-beat cardiovascular (CV) variability reflects the dynamic interactions between different components of the CV system, as well as the interplay between the CV system and neurally mediated regulatory mechanisms [1]. Time series analysis of CV variability can help our understanding of the underlying signal generating mechanisms and detect CV diseases [2, 3]. There is also an increasing interest in the application of CV variability monitoring to improve the clinical outcomes [4].

Traditional CV variability analysis mainly employed univariate time series. This is only applicable if all the time series are independent or uncorrelated, which is often not the case. However, the human system is very complex with different interactions between components [5]. There are therefore substantial advantages in simultaneously analyzing multivariate time series observed from the CV system, especially if there is a large degree of uncertainty of the underlying system [6, 7].

Several multivariate CV time series studies have been reported, including evaluation of the differences between heart rate variability and blood pressure variability [3], between systolic and diastolic interval variability [8], between cardiac and respiratory systems [9], and between multi-site pulse oximeter data [10]. However, they focused only on the interaction between two time series, and there is no known study to compare the difference between using univariate and multivariate time series.

The aim of this study was to assess the difference of CV variability between normal and congestive heart failure (CHF) subjects using both univariate and multivariate series. A recently developed multivariate sample entropy (MSE) method [6, 7] was used.

2. Methods

2.1. Subjects

30 normal (16 male and 14 female) and 30 CHF (21 male and 9 female) subjects were studied, aged between 20 and 75 years old. This study obtained a full approval from the Clinical Ethics Committee of Qilu Hospitals of Shandong University. The investigation conformed to the principles in the Declaration of Helsinki.

The CHF subjects were in classes II-III of the New York Heart Association with functional classification confirmed by an ultrasonic cardiogram and has a left ventricular ejection fraction (LVEF) less than 50%. The normal subjects had a LVEF between 58-81% and also had normal results with blood lipid, glucose and electrocardiogram (ECG) checks. The demographic information is given in Table 1.

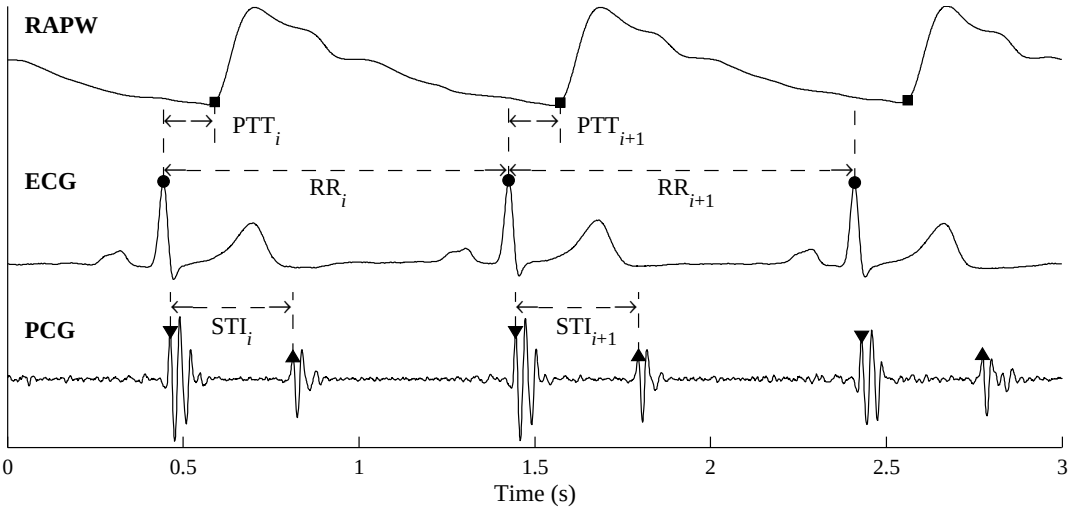

Figure 1. Simultaneously recorded ECG, phonocardiogram (PCG) and radial artery pressure waveforms (RAPW) signals. The detected R-wave peaks are denoted as "●", the first heart sounds produced by the closing of left artroventricular valve (bicuspid) and the second sounds produced by the closing of aortic valve are denoted as "▼" and "▲" respectively, the foot points of RAPW signals are denoted as "■".

Table 1. Demographic data for the subjects studied. Their means and standard deviations (SDs) are presented.

Variables	Normal	CHF	*P*-values
Age (year)	56 ± 9	59 ± 8	0.1
Height (cm)	166 ± 8	168 ± 10	0.5
Weight (kg)	65 ± 7	67 ± 8	0.4
HR (beats/min)	67 ± 9	71 ± 11	0.1
SBP (mmHg)	120 ± 12	123 ± 10	0.5
DBP (mmHg)	69 ± 10	70 ± 8	0.8
LVEF (%)	68 ± 5	39 ± 7	<0.001

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction.

2.2. Experimental procedure

All the measurements were undertaken in a quiet, temperature controlled clinical measurement room (25 ± 3°C) at Qilu Hospital of Shandong University. Before the formal signal recording, each subject lay supine on a measurement bed for a 10 min rest period to allow CV stabilization. Manual auscultatory systolic and diastolic blood pressures (SBP and DBP) were recorded at the beginning and end of the signal recording. The average SBP and DBP from the two measurements were used as reference BPs. The overall means and standard deviations (SDs) of SBP and DBP are also given in Table 1.

Standard limb lead-II ECG, phonocardiogram (PCG) and radial artery pressure waveforms (RAPW) were simultaneously recorded at a sample rate of 1000 Hz for 10 min for each subject. Subjects were told to breathe regularly and gently during the measurement. Figure 1 gives a typical example of these signals.

2.3. Signal processing

Band-pass Butterworth filters were used for ECG (0.5-125 Hz), PCG (20-200 Hz) and RAPW (0.05-45 Hz) signals respectively. Different feature points of the three signals were then identified, as shown in Figure 1. Finally, time series of RR interval (between consecutive R-wave peaks), cardiac systolic time interval (STI, the interval between the first and second heart sounds) and pulse transit time (PTT, between the R-wave peak of the ECG and the foot of RAPW), were constructed. Figure 2 gives an example of the three constructed time series from a normal subject for 300 beats.

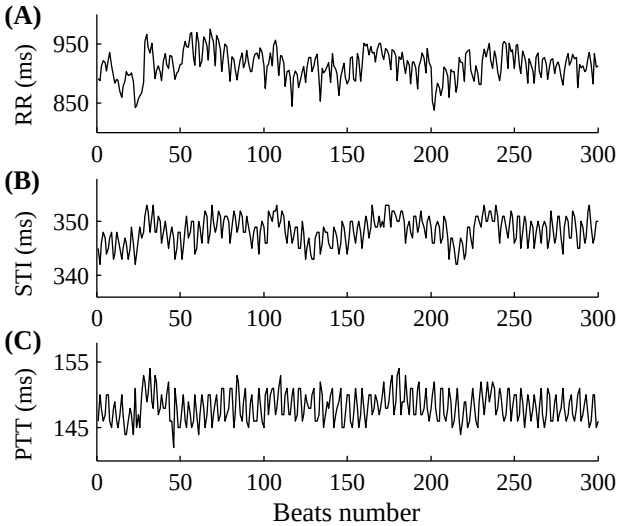

Figure 2. Example of RR, STI and PTT series from a normal subject for 300 beats.

2.4. Multivariate sample entropy

MSE method was recently developed from sample entropy (SampEn) by Ahmed and Mandic [6, 7]. The main steps include:

(1) For a *p*-variate time series $\{x_{k,i}\}_{i=1}^{N}, k=1,2,\cdots,p$, where *N* is the number of samples in each variate, firstly normalize each time series for $k=1,2,\cdots,p$, then form the composite delay vector using a composite delay factor based on the multivariate embedded reconstruction:

$$X_m(i)=[x_{1,i},x_{1,i+\tau_1},\cdots,x_{1,i+(m_1-1)\tau_1},x_{2,i},x_{2,i+\tau_2},\cdots, x_{2,i+(m_2-1)\tau_2},\cdots,x_{p,i},x_{p,i+\tau_p},\cdots,x_{p,i+(m_p-1)\tau_p}], \quad (1)$$

where $M=[m_1,m_2,\cdots,m_p]\in \mathbb{N}^p$ is the embedding vector, $\tau=[\tau_1,\tau_2,\cdots,\tau_p]\in \mathbb{N}^p$ the time lag vector, and $X_m(i)\in \mathbb{R}^m$ is the composite delay vector, where $m=\sum_{k=1}^{p}m_k$, $i=1,2,\cdots,N-n$ and $n=\max(M)\times\max(\tau)$.

(2) Define the distance between any two composite delay vectors $X_m(i)$ and $X_m(j)$ as the maximum norm, that is,

$$d[X_m(i),X_m(j)]=\max_{l=1,2,\cdots,m}(|x(i+l-1)-x(j+l-1)|)$$

.

(3) For a given composite delay vector $X_m(i)$ and a threshold *r*, count the number of instances P_i where $d[X_m(i),X_m(j)]\le r$, $j\ne i$, then calculate the frequency of occurrence, $B_i^m(r)=(N-n-1)^{-1}P_i$, and define a global quantity $B^m(r)=(N-n)^{-1}\sum_{i=1}^{N-n}B_i^m(r)$.

(4) Extend the dimensionality of the multivariate delay vector in (1) from *m* to (*m*+1). This can be performed in *p* different ways, as the system can evolve to any space with $M=[m_1,m_2,\cdots,m_k+1,\cdots,m_p]$ ($k=1,2,\cdots,p$). Thus, a total of $p\times(N-n)$ vectors $X_{m+1}(i)\in \mathbb{R}^{m+1}$ are obtained.

(5) For a given $X_{m+1}(i)$, count the number of instances Q_i where $d[X_{m+1}(i),X_{m+1}(j)]\le r$, $j\ne i$, then calculate the frequency of occurrence, $B_i^{m+1}(r)=(p(N-n)-1)^{-1}Q_i$, and define $B^{m+1}(r)=(p(N-n))^{-1}\sum_{i=1}^{p(N-n)}B_i^{m+1}(r)$.

(6) Finally, MSE is defined by

$$\mathrm{MSE}(M,\tau,r,N)=-\ln[B^{m+1}(r)/B^m(r)]. \quad (2)$$

MSE is the same as the traditional univariate sample entropy when $p=1$. In this study, we set $p=1,2,3$ to respectively measure the MSE values from the univariate, bivariate and trivariate time series. The original RR, STI and PTT series had the same length of $N=300$. The other parameters setting are: $m_k=2$ and $\tau_k=1$ for $k=1,2,\cdots,p$, and *r* equals 0.15 times the series SD. The CV time series used for MSE analysis are summarized as:

- Univariate: RR, STI and PTT;
- Bivariate: RR & STI, RR & PTT and STI & PTT;
- Trivariate: RR & STI & PTT.

2.5. Statistical analysis

The overall means and SDs of MSE were obtained separately for normal and CHF subjects. The differences between the two groups were compared using a student's *t*-test (SPSS 19.0 software package). A value of $P<0.05$ was considered statistically significant.

3. Results

Figure 3 and Table 2 give the MSE results from the univariate, bivariate and trivariate time series for both normal and CHF groups. All MSE values in the CHF group were significant lower than those in the normal group (all $P<0.05$, except for the univariate PTT series $P=0.49$).

The difference between the two subject groups was more statistically significant from multivariate (bivariate or trivariate) time series than that from univariate time series (with $P<0.05$ to $P<0.001$, see Figure 3).

For both normal and CHF groups the mean MSE values decreased from using univariate to multivariate time series (Figure 3 and Table 2).

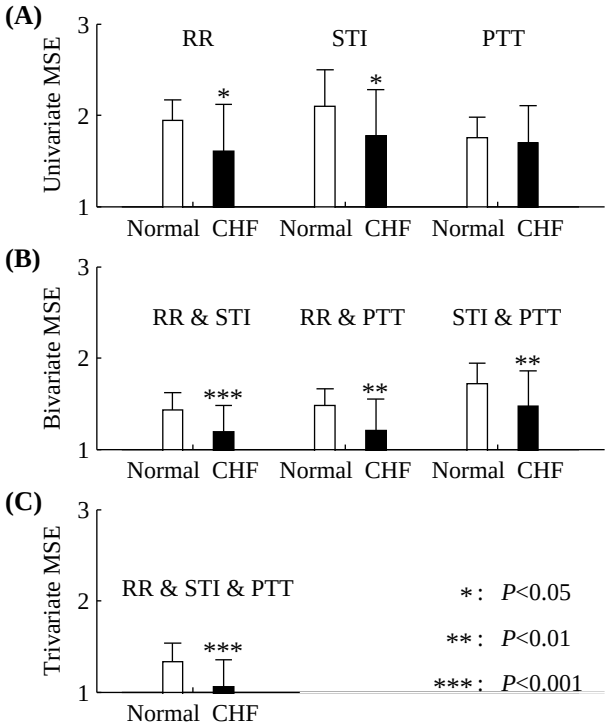

Figure 3. Statistical results of the univariate MSE (A), bivariate MSE (B) and trivariate MSE (C) for the normal and CHF groups.

4. Discussion

The decrease of the univariate MSE in the CHF group

confirms the significant complexity loss in RR and STI series for CHF subjects. CHF has a loss of cardiac pumping function [11, 12]. Lower STI MSE in the CHF group indicates damage of cardiac pumping function. In addition, the complexity loss of the RR series is usually regarded as the decrease of nerve regulation for the CV system. So the lower RR MSE in the CHF group confirms dysfunction of nerve regulation with CHF [11, 13]. Although the cardiac pumping function (directly reflected by index LVEF) has a significant difference between the two groups, the blood pressures (SBP and DBP) have no significant differences. So from the fact that the PTT MSE has no significant difference between the two groups, it could be inferred that the complexity of the PTT series is more closely related to the arterial function rather than cardiac function. The bivariate and trivariate MSE values in the CHF group were also significantly lower than those in the normal group, indicating that the increase of the cross-channel synchronization.

Table 2. Results (mean ± SD) and statistical *P*-values of the univariate and multivariate MSE for the two groups.

Time series	Normal	CHF	*P*-values
Univariate			
RR	1.9 ± 0.2	1.6 ± 0.5	<0.05
STI	2.1 ± 0.4	1.8 ± 0.5	<0.05
PTT	1.8 ± 0.2	1.7 ± 0.4	0.49
Bivariate			
RR & STI	1.5 ± 0.2	1.2 ± 0.3	<0.001
RR & PTT	1.5 ± 0.2	1.2 ± 0.4	<0.01
STI & PTT	1.7 ± 0.2	1.5 ± 0.4	<0.01
Trivariate			
RR & STI & PTT	1.3 ± 0.2	1.0 ± 0.3	<0.001

When using the multivariate (bivariate or trivariate) MSE, the statistical significances between the two groups increased, confirming that the multivariate analysis could give a better understanding of the CV system dynamics [6, 7]. It is also worth to note that the mean MSE values decreased from using univariate to multivariate time series for both normal and CHF groups. This is mainly due to the constant threshold r of 0.15 times the series SD. The series SD will become p when using p-variate series. However, the frequency of vector similarity of p-variate series rarely becomes that from the sum value of the univariate time series. So the multivariate MSE will decrease as the number of channels increase.

5. Conclusion

This study used the MSE method to analysis both the univariate and multivariate CV time series variability and to compare the differences between the normal and CHF groups. The results indicate that the complexity of univariate series decrease and the synchronization of multivariate series increase for CHF subjects.

Acknowledgement

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