Coupling between Short-Term Heart Rate and Diastolic Period is Reduced in Heart Failure Patients as Indicated by Multivariate Entropy Analysis

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Abstract

The analyses of cardiac dynamics appear to be very promising in assessing cardiovascular health. Short-term analysis well meets the increasing clinical needs for point-of-care diagnosis, portable monitoring and personal healthcare. In one of our previous CinC articles, we have shown that there is inherent coupling between short-term heart rate variability (HRV) and diastolic period variability (DPV). Besides, the coupling is reduced at their small temporal scales in healthy aging subjects. We thus aimed to investigate the HRV–DPV coupling in heart failure (HF) patients in this work.

Fifty healthy volunteers and 52 HF patients were studied. Multiscale multivariate fuzzy entropy (MMFE) analysis was performed in each bivariate signal (short-term HRV and simultaneous recorded DPV) to probe into their within- and cross-channel correlations. Results show that the coupling between short-term HRV and DPV is reduced at both small and large temporal scales in HF patients compared with healthy volunteers. It may indicate that the heart loses both the immediate mechanical response to the changes of heart period and its long-range compliance, which is very different from the effects of healthy aging. It thus shows great potential of short-term HRV–DPV coupling analysis in the noninvasive and nondestructive detection of HF. An increased specificity of the so-constructed HF detection indices should also be expected.

1. Introduction

It is a contemporary challenge to timely and accurately recognize the cardiovascular deterioration in multi-parameter monitoring. Short-term cardiac dynamics analysis appears to be able to provide promising tools for immediately detecting the abnormalities [1].

In one of our last CinC articles [2], we have defined the diastolic period variability (DPV) from the radial artery pressure waveform (RAPW) to represent the beat-to-beat variation of the cardiac diastole. We have found that the heart rate variability (HRV) is preferentially expressed in DPV. There is an inherent coupling between them. However, the coupling is reduced at small temporal scales with healthy aging.

The study aimed to probe into the variation of HRV–DPV coupling in heart failure (HF) patients. We hypothesized that the coupling was reduced in HF patients at both small and large temporal scales.

2. Methods

2.1. Subjects

Sixty HF patients (NYHA class: II~III) aged between 40 and 75 and 60 healthy volunteers aged between 23 and 72 were enrolled, among which the healthy subjects have been reported in our last CinC article [2]. Eight HF patients and 10 healthy volunteers were excluded in this study to ensure age and gender comparability. Written informed consent was requested prior to participation. This study has obtained full approval from the Clinical Ethics Committee of the Qilu Hospital of Shandong University. Their characteristics are presented in Table 1.

Table 1. Subjects characteristics.

Variables	Healthy subjects	HF patients
No.	50 (22/28)	52 (30/22)
Age (years)	56.5 ± 7.6	59.8 ± 10.6
Height (cm)	165 ± 7.4	168 ± 5.3
Weight (kg)	62.3 ± 9.5	66.0 ± 9.0
HR (beats/min)	67 ± 7	70 ± 10
SBP (mmHg)	118 ± 13	120 ± 8
DBP (mmHg)	70 ± 10	71 ± 7

DBP diastolic blood pressure, *HR* heart rate, *No*. number, *SBP* systolic blood pressure. Date are expressed as number (male/female) or mean ± SD.

2.2. Protocol

Measurements were undertaken in a quite temperature controlled clinical measurement room (25 ± 3 °C) at Qilu

Hospital of Shandong University, by a Cardiovascular Function Detection device (CV FD–I) produced by Huiyironggong Tech. Co. Ltd., Jinan, PR China. Each subject lay supine on a measurement bed for a 10 min rest period before the formal recording to allow cardiovascular stabilization. ECG electrodes were attached to the right wrist, the right and left ankles to acquire a standard lead–II ECG. A piezoresistive sensor was attached to the left wrist to acquire the RAPW signal. Subjects were told to breathe regularly and gently during the whole measurement procedure.

2.3. Signal acquisition and preprocessing

ECG and RAPW signals were recorded synchronously in each subject at a sampling frequency of 1 kHz for 5 min. To facilitate off-line analysis, customized program was designed by MATLAB software (Ver. R2013a, Mathworks, USA). R-wave locations in ECG were detected automatically and ectopic R-wave were removed by a data-adaptive template matching procedure [3]. HRV series were constructed by consecutive non-ectopic RR intervals. The systolic feet and dicrotic notches in RAPW were detected by the first-order differential signals [4]. DPV series were constructed by intervals between the dicrotic notches and the following systolic feet. Note that the corresponding diastolic interval of an ectopic beat should also be removed in DPV series.

2.4. Multivariate entropy analysis

In order to account for both within- and cross-channel dependencies in multiple data channels and over multiple temporal scales, Ahmed and Mandic have established a multiscale multivariate sample entropy (MMSE) measure [5]. We have recently proved that MMSE is capable of quantifying nonlinear coupling in simulation models [6]. A geometrical explanation of the coupling patterns captured by MMSE in bivariate data can be found in [5].

To improve the stability and consistency, we have recently refined MMSE by substituting a novel fuzzy membership function for the hard threshold. The so-constructed multiscale multivariate fuzzy entropy (MMFE) has been showed to be significantly improved in performances [7]. We thus here in this study employed MMFE to investigate the coupling between HRV and DPV. The MMFE algorithm can be summarized as follows.

1) For p-channel sequences $\{y_{k,j}\}$, $k=1,2,\cdots,p$, $j=1,2,\cdots,N$, their counterparts at scale ε can be expressed as

$$x_{k,i}^{\varepsilon}=\frac{1}{\varepsilon}\sum_{i=(j-1)\varepsilon+1}^{j\varepsilon}y_{k,j},\ 1\le j\le\lfloor N/\varepsilon\rfloor. \tag{1}$$

2) At each scale ε, form composite delay vectors

$$\mathbf{X}_m^{\varepsilon}(i)=\left\{x_{1,i}^{\varepsilon},x_{1,i+1}^{\varepsilon},\cdots,x_{1,i+(m_1-1)}^{\varepsilon},x_{2,i}^{\varepsilon},\cdots,x_{2,i+(m_2-1)}^{\varepsilon},\right.$$
$$\left.,x_{p,i}^{\varepsilon},\cdots,x_{p,i+(m_p-1)}^{\varepsilon}\right\}=\left\{z_i^{\varepsilon},z_{i+1}^{\varepsilon},\cdots,z_{i+m-1}^{\varepsilon}\right\}, \tag{2}$$

where $m=\sum_{k=1}^{p}m_k$, $i=1,2,\cdots,N^{\varepsilon}-n$, $n=\max\{\mathbf{M}\}$, $\mathbf{M}=\{m_1,m_2,\cdots,m_p\}$ and $N^{\varepsilon}=\lfloor N/\varepsilon\rfloor$.

3) Define the distance between any two composite delay vector $\mathbf{X}_m^{\varepsilon}(i)$ and $\mathbf{X}_m^{\varepsilon}(j)$ as the maximum norm, that is $d\{X_m^{\varepsilon}(i),X_m^{\varepsilon}(j)\}=\max_{l=1}^{m}\{|z_{i+l-1}^{\varepsilon}-z_{j+l-1}^{\varepsilon}|\}$.

4) For a given threshold value r, define a global quantity $B^m(r)$ as the average membership grade of $d\{\mathbf{X}_m^{\varepsilon}(i),\mathbf{X}_m^{\varepsilon}(j)\}$, that is

$$B^m(r)=\frac{1}{N^{\varepsilon}-n}\sum_{i=1}^{N^{\varepsilon}-n}\frac{\sum_{j=1}^{N^{\varepsilon}-n-1}\Theta\left(d\{\mathbf{X}_m^{\varepsilon}(i),\mathbf{X}_m^{\varepsilon}(j)\},r\right)}{N^{\varepsilon}-n-1}, \tag{3}$$

where $\Theta(d,r)$ is a fuzzy membership function which can be expressed as

$$\Theta(d,r)=\begin{cases}1, & (0\le d\le r)\\ e^{-\ln(2)\left(\frac{d-r}{r}\right)^2}, & (d>r)\end{cases}. \tag{4}$$

5) Extend the dimensionality from m_k to m_k+1. Note that this can be performed in p different ways and the readers can refer to [5] for details. Thus $p\times(N^{\varepsilon}-n)$ vectors $X_{m+1}^{\varepsilon}(i)$ are obtained. Define the quantity $B^{m+1}(r)$ in a similar means as has employed in step 4).

6) Define MMFE at scale ε as the negative of a natural logarithm of the ratio of $B^{m+1}(r)$ and $B^m(r)$, that is

$$\mathrm{MMFE}(\varepsilon)=-\ln\frac{B^{m+1}(r)}{B^m(r)}. \tag{5}$$

HRV and DPV series after anomalous removal were used for this analysis. They were normalized first by their corresponding standard deviation. Parameter **M** was set at [2, 2], r at 0.12 and $\varepsilon=5$.

2.5. Statistical analysis

MMFE values between HF patients and healthy volunteers were compared at each temporal scale using Mann–Whitney *U* test as the Kolmogorov–Smirnov test had revealed a non-normal distribution for MMFE results. Statistical significance was accepted at $p<0.05$. All statistical analyses were performed using the SPSS software (Ver. 20.0, IBM, USA).

3. Results

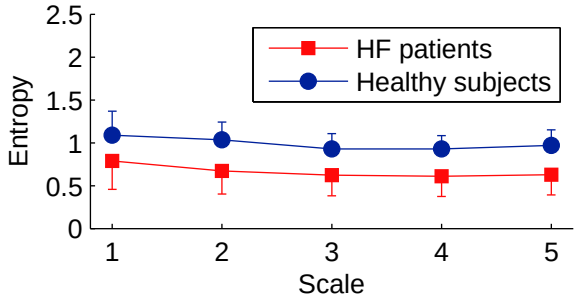

Figure 1. MMFE analysis of bivariate (HRV, DPV) signals in HF patients and healthy subjects. The curves represent the average of each group and error bars the standard deviation.

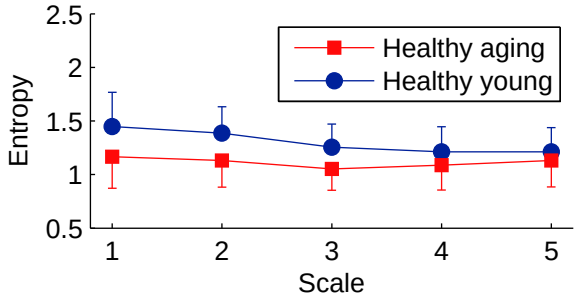

Figure 2. MMFE analysis of bivariate (HRV, DPV) signals in healthy aging and healthy young groups. The curves represent the average of each group and error bars the standard deviation. Results were adapted from [2]. The aging subjects were aged from 50 to 72 years and young subjects from 23 to 49 years.

Table 2. Results of Mann-Whitney *U* tests.

	p				
	scale 1	scale 2	scale 3	scale 4	scale 5
a vs. b	<0.05	<0.01	<0.01	<0.01	<0.01
c vs. d	<0.01	<0.01	<0.01	0.09	0.30

a HF patients, *b* healthy subjects, *c* healthy aging, *d* healthy young.

Figure 1 shows the MMFE results of HRV–DPV coupling in HF patients compared with healthy subjects. Results of Mann-Whitney *U* tests at each scale between the two groups are showed in Table 2. The coupling is significantly reduced in HF patients at each group.

For comparison purposes, we adapted the results in our last CinC article [2] as shown in Figure 2. In the mentioned study, we have investigated the HRV–DPV coupling at each temporal scale as functions of age. Here we divided the results into two groups–one was the healthy aging group aged from 50 to 72 and the other the healthy young group aged from 23 to 49. The Mann-Whitney *U* tests were also performed at each temporal scale and the results were summarized in Table 2. The HRV–DPV coupling was reduced significantly only at small temporal scales (scale 1~3) in healthy aging group compared with healthy young group. No significant variations were shown at large temporal scales (4 and 5) between these two groups.

4. Discussion and conclusion

The coupling between short-term HRV and DPV is reduced in HF patients at both small and large temporal scales as indicated by MMFE analysis. The observations strongly support our hypothesis.

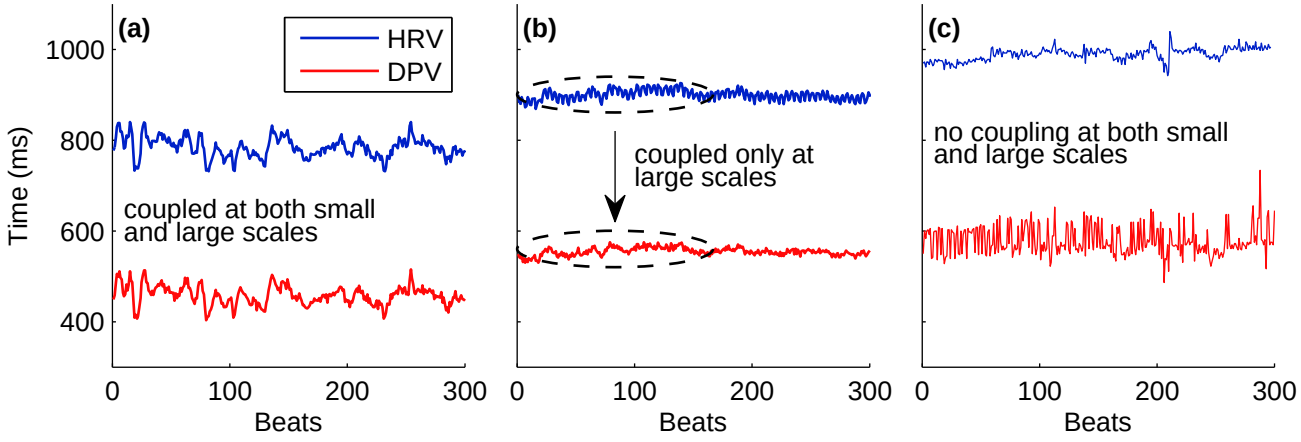

Figure 3. HRV and DPV series in one male healthy subject aged 23 **(a)**, one male healthy subjects aged 61 **(b)**, and one male HF patient aged 70 **(c)**. Only the first 300 points in each series were shown for comparison purposes.

Signals at small temporal scales of HRV and DPV reveal their high frequency components. They are coupled to each other, indicating that the beat-to-beat systole is relatively stable in healthy young subjects. Thus it can support steady, adequate stroke volume in each cardiac cycle, so as to guarantee that the peripheral organs get steady-going blood supplies. Their large-scale components (low-frequency trend) are also coupled in healthy young subjects, which maybe suggest that the cardiac has a long-range mechanical compliance, making the diastole capable of adapting to the sino-atrial activity.

The decrease of coupling at small scales in healthy aging subjects maybe suggests that the cardiac loses the ability of immediate mechanical response to the change in the electrical pacing period. The beat-to-beat stroke volume may not be constant consequently. This assumption can be further examined by measurement or estimation of beat-to-beat stroke volume. Readers can refer to a most recent systematic review on related techniques [8]. But the unchanged long-range coupling of HRV and DPV reveals that the blood supplies should still be steady in terms of, for instance, cardiac output. It can support the peripheral blood requirements to some extent. However, the relatively unstable cardiac systole should probably raise its vulnerability. Our results might reveal a clue to the fact that healthy aging increases the absolute cardiovascular risks.

The HRV–DPV coupling is reduced in HF patients at both small and large temporal scales, indicating a highest cardiac vulnerability. The cardiac not only loses the ability of immediate mechanical response but also the long-range mechanical adaptability to the heart period. The maladjustment between the cardiac mechanical and electrical activities in HF patients thus cannot support the peripheral organs steady and adequate blood perfusion and sufficient oxygen supplies. Thus, it should exhibit common clinical symptoms of dyspnea in HF patients.

The coupling between HRV and DPV in healthy young subjects or decoupling in healthy aging and HF patients can manifest itself in the time-domain waveforms. Figure 3 shows the HRV and DPV waveforms in one healthy male subject aged 23, one healthy male subject aged 61, and one male HF patient aged 70, respectively. Apparently we can spot that the HRV and DPV are almost synchronized to each other in both the very details (high-frequency components) and the trends (low-frequency components) in healthy young subject as shown in Figure 3 **(a)**. Details of HRV and DPV are desynchronized whereas their low-frequency trends are still coupled in the healthy aging subject in Figure 3 **(b)**. No coupling is showed in both details and the trends in the HF patient in Figure 3 **(c)**. In addition, the DPV series in Figure 3 **(c)** has relatively large fluctuations, which also indicates that the cardiac systole is no longer stable in HF patients. It should be noted that not all the subjects have such apparent linear coupling or decoupling. Long range within- and cross-channel correlations are relatively more common in such complex physiological series. It is generally one main concern that we employed the MMFE analysis in this study.

To summarize, this study shows that the HRV–DPV coupling is reduced in HF patients. It is different from the aging effects that the depression of the coupling in HF patients appears at both small and large temporal scales. The results show very promising in the noninvasive and nondestructive detection of HF. An increased specificity in HF detection should also be expected as the mentioned approach can eliminate the influence of healthy aging.

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