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The Factors Influence Compatibility of Pulse-Pulse Intervals with R-R Intervals

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***Abstract*—Cardiac autonomic dysfunction assessed by power spectral analysis of electrocardigographic (ECG) R-R intervals (RRI) is a useful method in clinical research. The compatibility of pulse-pulse intervals (PPI) acquired by photoplethysmography (PPG) with RRI is equivocal. In this study, we would like to investigate factors influence the compatibility. We recruited 25 young and health subjects divided into two groups: normal subjects (Group1, BMI < 24, n=15) and overweight subjects (Group2, BMI ≧24, n=10). ECG and PPG were measured for 5 minutes. Used cross-approximate entropy (CAE) and Fast Fourier transform (FFT) to obtained compatibility between RRI and PPI. The CAE value in Group1 were significantly lower than in Group2 (1.71 ± 0.12 *vs*. 1.83 ± 0.11, *P* = 0.011). A positive linear relationship between CAE value and risk factors of metabolic syndrome. No significantly difference between LFP/HFP ratio of RRI (LHR_{RRI}) and LFP/HFP ratio of PPI (LHR_{PPI}) in Group1 (1.42 ± 0.19 *vs*. 1.38 ± 0.17, *P* = 0.064), LHR_{RRI} significantly higher than LHR_{PPI} in Group2 (2.18 ± 0.37 vs. 1.93 ± 0.30, *P* = 0.005). It should be careful that using PPI to assess autonomic function in the obese subjects or the patients with metabolic syndrome.**

I. Introduction

Heart rate variability (HRV) is the beat-to-beat oscillation modulated by sympathetic and parasympathetic nerves [1]. Changes of HRV indicate cardiac autonomic dysfunction and predict grave prognosis in patients with or without structural heart diseases [2]. The imbalanced situations are also found in diabetic neuropathy or unrecognized autonomic dysfunction [3]. Initially, HRV are measured by analyzing R-R intervals (RRI) on electrocardiographic (ECG) recording. They are currently available in many commercial devices and have been used for clinical research widely.

Photoplethysmography (PPG) is an optical technique used to monitor blood volume changes in the microvascular bed of tissue [4]. The progress in semiconductor technology and optoelectronics facilitate to application of PPG to become one of the most popular methods in clinical monitor of pulse rates, blood pressure and oxygen saturation [5]. To measure pulse-pulse interval (PPI) by using PPG is another approach to assess cardiac autonomic function. In contrast to ECG, acquisition of pulse signals can be traced with a single sensor without any electrode with neither the inconvenience of installation nor the examinee to be undressed. Furthermore, ECG recording for RRI analysis still has some drawbacks such as noise generated by surface electromyography, respiration induced baseline drift, power line interference and electrode contact movement. Besides, morphological variation in ECG waveform and heterogeneity of QRS complex often make it difficult to identify R waves [6]. An investigator has used PPI as an alternative for analyzing HRV [7] . However, some researchers suggested that the pulse rate variability derived from PPG is not a surrogate for HRV analysis [8], [9]. Recently, a comprehensive review article suggested that HRV analyses by PPI and RRI may differ from each other during a short-term recording [10]. In addition to diverse experiment settings and methods of analysis, we would like to investigate the factors those influence compatibility of PPI with RRI for HRV analysis.

We recruited 25 healthy young subjects. RRI and PPI were recorded by ECG and PPG on the left index finger respectively. The similarity of RRI and PPI were quantified with by cross-approximate entropy (CAE). Association between CAE value and factors including waist circumference, systolic blood pressure, diastolic blood pressure, body mass index (BMI) were analyzed.

II. Materials and Methods

A. Subjects and Protocol

This study recruited 25 young and health subjects from Hualien Hospital, Taiwan between July, 2009, and October, 2012. All subjects were recruited from adult health examinations. The blood tests administered to each subject including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, cholesterol, glycosylated, hemoglobin (HbA1c) and fasting blood sugar. All of the subjects were required to fill out a questionnaire regarding their lifestyle, smoking habits, and medical history as well as sign a consent form.

According to the Bureau of Health Promotion, Department of Health, Executive Yuan, Taiwan, the definition of obesity among Taiwanese is BMI higher than 24 kg/m^2. The 25 subjects were then divided into two groups: normal subjects (Group1, BMI < 24 kg/m^2, n=15) and overweight subjects (Group2, BMI ≧24 kg/m^2, n=10). The study was approved by the Institutional Review Board (IRB) of Hualien Hospital. All subjects refrained from caffeine-containing beverages and theophylline-containing medication for 8 hours prior to each hospital visit. Blood pressure was obtained once over the left arm of the supine subjects using an automated

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oscillometric device (BP3AG1, Microlife, Taiwan) with a cuff of appropriate size.

All subjects were permitted to rest in a supine position in a quiet, temperature-controlled room at 25 ± 1℃ for 3 minutes prior to subsequent 5-minute measurements of ECG and PPG simultaneously.

B. The Agreement Between PPI and RRI

As shown in Fig. 1, ECG measurements were obtained using the conventional method. Because of its conspicuousness, the R wave in Lead II was selected, and infrared sensors were obtained from the second finger of left hand. After being processed through an analog-to-digital converter (USB-6009 DAQ, National Instruments, Austin, TX) at a sampling frequency of 500 Hz, the digitized signals were stored in a computer. The time difference between the two consecutive peak of ECG R wave was defined as $RRI(i)$, and the time difference between the two consecutive peak of PPG was defined as $PPI(j)$.

C. Cross-Approximate Entropy of RRI and PPI

Due to a trend within physiological signals [11], non-zero means may be included; therefore, we used empirical mode decomposition (EMD) [12] to deconstruct the $\{RRI(i)\}$ and $\{PPI(j)\}$ series, thereby eliminating the trend from the original series. We then normalized the $\{RRI(i)\}$ and $\{PPI(j)\}$series, as shown in (1) and (2). In these equations, SD_x and SD_y represent the standard deviations of series $\{RRI(i)\}$ and $\{PPI(j)\}$, respectively. Complexity analysis was performed on the normalized results, $\{RRI'(i)\}$ and $\{PPI'(j)\}$.

$$\{RRI'(i)\}=\frac{\{RRI(i)\}}{SD_x} \tag{1}$$

$$\{PPI'(j)\}=\frac{\{PPI(j)\}}{SD_y} \tag{2}$$

A previous study [13] has used CAE, an improved analysis method of approximate entropy, to analyze two synchronous physiological time series, define their relationship, and calculate the complexity within that relationship [14]. This method employs the dynamic changes between the two series to evaluate the physiologic system. Similarities between changes in the two series can be used to observe the regulatory mechanisms in the physiologic system. The details of the algorithm are as follows [15].

1. For given m, for two sets of m-vectors,

$$x(i)\equiv\left[RRI'(i)\quad RRI'(i+1)\quad \ldots\quad RRI'(i+m-1)\right]$$
$$i=1,N-m+1, \tag{3}$$
$$y(j)\equiv\left[PPI'(j)\quad PPI'(j+1)\quad \ldots\quad PPI'(j+m-1)\right]$$
$$j=1,N-m+1. \tag{4}$$

2. Define the distance between the vectors $\mathbf{x}(i)$, $\mathbf{y}(j)$ as the maximum absolute difference between their corresponding elements, as follows:

$$d[x(i),\ y(j)]=\max_{k=1}^{m}[|RRI'(i+k-1)-PPI'(j+k-1)|]. \tag{5}$$

3. With the given $\mathbf{x}(i)$, find the value of $d[x(i),\ y(j)]$ (where j = 1 to $N-m+1$) that is smaller than or equal to r and the ratio of this number to the total number of m-vectors ($N-m+1$). That is, let $N^m_{RRI'PPI'}(i)$ = the number of $\mathbf{y}(j)$ satisfying the requirement $d[x(i),\ y(j)] \leqq r$, then

$$C^m_{RRI'PPI'}(i)=\frac{N^m_{RRI'PPI'}(i)}{N-m+1}. \tag{6}$$

$C^m_{RRI'PPI'}(i)$ measures the frequency of the m-point PPI' pattern being similar (within a tolerance of ± r) to the m-point RRI' pattern formed by $\mathbf{x}(i)$.

4. Average the logarithm of $C^m_{RRI'PPI'}(i)$ over i to obtain $\phi^m_{RRI'PPI'}(r)$, as follows:

$$\phi^m_{RRI'PPI'}(r)=\frac{1}{N-m+1}\sum_{i=1}^{N-m+1}\ln C^m_{RRI'PPI'}(i). \tag{7}$$

5. Increase m by 1 and repeat steps 1~4 to obtain $C^{m+1}_{RRI'PPI'}(i)$, $\phi^{m+1}_{RRI'PPI'}(r)$.

6. Finally, take $CAE_{RRI'PPI'}(m,r)=\lim_{N\to\infty}\left[\phi^m_{RRI'PPI'}(r)-\phi^{m+1}_{RRI'PPI'}(r)\right]$ and for N-point data, the estimate is

$$CAE_{RRI'PPI'}(m,r,N)=\phi^m_{RRI'PPI'}(r)-\phi^{m+1}_{RRI'PPI'}(r). \tag{8}$$

To ensure efficiency and accuracy of calculation, the parameters of this study were set at m = 2, r = 0.15, and N = 360.

D. Fast Fourier Transform of Herat Rate Variability

To assessment whether PPI can substitute RRI to assess autonomic function, we used FFT to analysis frequency domain of RRI and PPI. In the 0.04 - 0.15 Hz range, a low frequency power (LFP) was derived, while in the 0.15 - 0.4 Hz range, a high frequency power (HFP) was obtained [16]. In this study, the LFP/HFP ratio of RRI (LHR_{RRI}) and PPI (LHR_{PPI}) variation serves as an indicator of autonomic function [17].

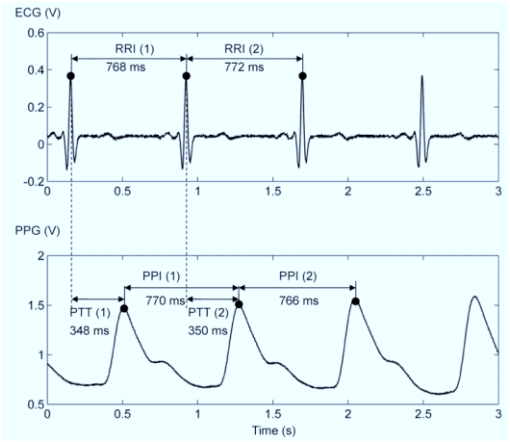

Figure 1. Measurements of electrocardiogram (ECG) and photoplethysmography (PPG) simultaneously; Obtained R wave to R wave interval (RRI) and pulse-pulse interval (PPI) from ECG and PPG, respectively.

E. Statistical analysis

Average values were expressed as mean ± SD. Significant differences in anthropometric, hemodynamic, and CAE value between two groups were determined using the Wilcoxon test. The significance difference between LHR_{RRI} and LHR_{PPI} in each groups was determined using the Mann-Whitney *U* test. The correlation between risk factors and CAE value was analyzed by using the Spearman correlation test. All statistical analyses were performed using Statistical Package for the Social Science (SPSS, version 14.0 for Windows. SPSS Inc. Chicago, II). A *P* value of < 0.05 was considered statistically significant.

III. Results

A. Comparisons of Parameters Between Normal and Overweight Subjects

Table I. displays significant differences between Group1 and Group2 in terms of body weight (65.19 ± 7.68 kg *vs.* 79.98 ± 8.40 kg, P = 0.001), waist circumference (78.40 ± 4.82 cm *vs.* 92.10 ± 7.61 cm, *P* < 0.001), BMI (22.02 ± 1.09 kg/m^2 *vs.* 26.75 ± 2.18 kg/m^2, *P* < 0.001) and SBP (113.93 ± 9.40 mmHg *vs.* 124.50 ± 9.22 mmHg, P = 0.009). Their blood samples also presented significant differences in triglyceride (58.00 ± 17.46 mg/dL *vs.* 126.90 ± 59.99 mg/dL, *P* = 0.001). There is no statistical significance of either LHR_{RRI} and LHR_{PPI} between Groups 1 and 2 (1.42 ± 0.73 *vs.* 2.18 ± 1.17, *P* = 0.085 and 1.38 ± 0.63 *vs.* 1.93 ± 0.94, *P* = 0.157, respectively). The CAE value in Group1 was significantly lower than that in Group2 (1.71 ± 0.12 *vs.* 1.83 ± 0.11, *P* = 0.011).

B. LHR_{RRI} and LHR_{PPI} in Each Groups

As shown in Fig. 2, no significantly difference between LHR_{RRI} and LHR_{PPI} in Group1 (1.42 ± 0.19 *vs.* 1.38 ± 0.17, *P* = 0.064), LHR_{RRI} significantly higher than LHR_{PPI} in Group2 (2.18 ± 0.37 *vs.* 1.93 ± 0.30, *P* = 0.005).

C. The Correlation Between CAE Value and Risk Factors

Fig. 3 shows that in all subjects, waist circumference (r = 0.448, *P* = 0.025), BMI (r = 0.448, *P* = 0.025) and triglyceride (r = 0.422, *P* = 0.036) presented a significantly positive linear relationship with CAE value, respectively. No significantly correlation in body weight, SBP with CAE value.

IV. Discussion

Previous studies proposed difference between pulse rate variation (PRV) and HRV exists [8], [9]. To investigate the factors influence the compatibility of PPI with RRI we included 25 healthy young subjects divided into two groups (Group1 normal, BMI < 24 kg/m^2 and Group2 overweight BMI ≧24 kg/m^2). In this study, the cardiac autonomic function was indicated by LHR by using PPI and RRI. Table I showed that there is no significant difference between LHR_{PPI} and LHR_{RRI} in either group, although the ratios were higher in Group2. Similar result has been found in previous study. The obese subjects had higher HRV than the normal [18], but was not observed in children [19]. Therefore, that HRV could significant higher in the aged obese patients with comorbidity of ischemic heart disease, but not in the younger overweight subjects.

Fig. 2 shows there is significant difference between LHR_{PPI} and LHR_{RRI} in the overweight subjects, but not in the normal. We used CAE to investigate the similarity of PPI with RRI in each groups. Table I disclosed that the CAE value between PPI and RRI in Group1 is lower than that in Group2 (1.71 ± 0.12 *vs.* 1.83 ± 0.11, *P* = 0.011). There are several studies investigated the compatibility of PPI with RRI in autonomic function assessment. The results are equivocal. A comprehensive review article suggested that PPI may differ from RRI in short-term recording because the influence of respiration [10]. There is one article using approximate entropy to check similarity between PPI and RRI. It showed that there is no difference between these two parameters in ten healthy subjects [20]. Our study also demonstrated that PRV can be used as an alternative measurement for cardiac autonomic function for the people with normal BMI, but not for the obese subjects. Meanwhile, the CAE value correlated with BMI (r = 0.448, *P* = 0.025), waist circumference (r = 0.448, *P* = 0.025) and triglyceride positively (r = 0.448, *P* = 0.025) (Fig. 3). Therefore, factors associate with metabolic syndrome may influence compatibility of PPI with RRI. It is not only caused by pacing or pulse traveling (Fig. 1), but also caused by other factors those uncertain.

In conclusion, PRV can be an alternative assessment for cardiac autonomic function in normal subjects, but may not be used for the overweight or patients with risk of atherosclerosis or metabolic syndrome. Nevertheless, our study proposed that CAE value between PPI and RRI may be a useful indicator for detecting early changes of autonomic function or metabolic syndrome. Further detail study on these populations may be helpful to confirm this speculation.

TABLE I. Comparisons of Demographic, Anthropometricm and Serum Biochemical Parameters Between Normal and Overweight Subjects

	Group1 (n=15)	Group2 (n=10)	*P*-value
Age (year)	25.93 ± 5.30	27.00 ± 5.77	0.738
Body height (cm)	171.73 ± 7.87	172.80 ± 5.27	0.845
Body weight (kg)	65.19 ± 7.68	78.98 ± 8.40	0.001
Waist circumference (cm)	78.40 ± 4.82	92.10 ± 7.61	< 0.001
BMI (kg/m^2)	22.02 ± 1.09	26.75 ± 2.18	< 0.001
SBP (mmHg)	113.93 ± 9.40	124.50 ± 9.22	0.009
DBP (mmHg)	70.87 ± 6.36	75.90 ± 7.99	0.126
HDL (mg/dL)	47.13 ± 9.73	43.10 ± 9.90	0.373
LDL (mg/dL)	105.60 ± 35.01	114.40 ± 46.96	0.868
Cholesterol (mg/dL)	171.33 ± 36.47	181.90 ± 46.66	0.677
Triglyceride (mg/dL)	58.00 ± 17.46	126.90 ± 59.99	0.001
Fasting blood sugar (mg/dL)	90.73 ± 4.82	91.40 ± 6.26	0.617
HbA1c (%)	5.45 ± 0.24	5.48 ± 0.30	0.823
LHR_{RRI}	1.42 ± 0.73	2.18 ± 1.17	0.085
LHR_{PPI}	1.38 ± 0.63	1.93 ± 0.94	0.157
CAE value	1.71 ± 0.12	1.83 ± 0.11	0.011

Data are presented as the mean ± SD. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HbA1c = glycosylated hemoglobin; LHR_{RRI} = LFP/HFP ratio of R-R interval (RRI); LHR_{PPI} = LFP/HFP ratio of pulse-pulse interval (PPI); CAE value = cross-approximate entropy value between RRI and PPI

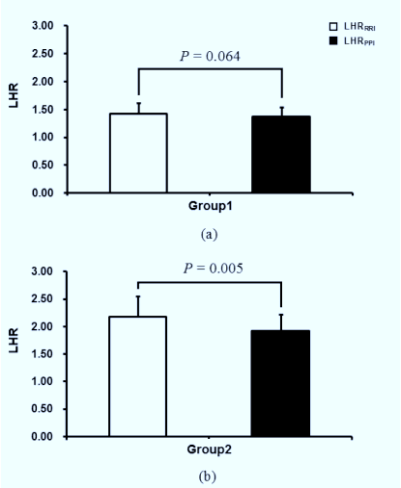

Figure 2. (a) No significant difference in LFP/HFP ratio of R-R interval (RRI) (LHR_{RRI}) and LFP/HFP ratio of pulse-pulse interval (PPI) (LHR_{PPI}) in normal subjects. (b) LHR_{PPI} was lower compared with LHR_{RRI} in overweight subjects. Data are presented as the mean ± standard error (given by $SD/\sqrt{n}$, where n is the number of subjects).

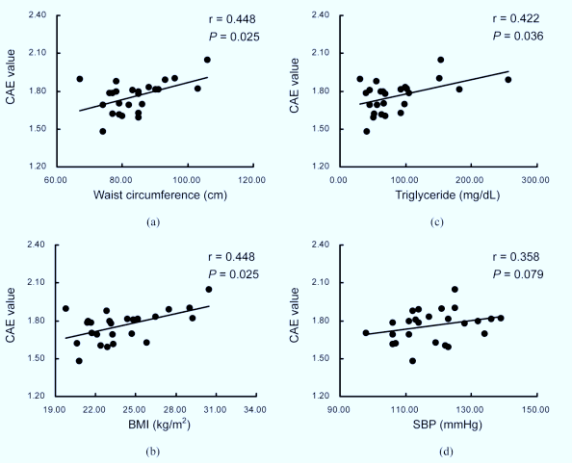

Figure 3.(a) Linear relationship between cross-approximate entropy (CAE) value and waist circumference; (b) Linear relationship between CAE value and body mass index (BMI); (c) Linear relationship between CAE value and triglyceride; (d) Linear relationship between CAE value and systolic blood pressure (SBP) in all subjects (n = 25).

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