Tzu Chi Medical Journal 2020; 32(1): 41–46

Original Article

Compatibility of pulse–pulse intervals with R–R intervals in assessing cardiac autonomic function and its relation to risks of atherosclerosis

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Submission : 16-Dec-2017
Revision : 12-Jan-2018
Acceptance : 23-Feb-2018
Web Publication : 20-Feb-2019

Abstract

Objective: Heart rate variability (HRV) analysis using electrocardiographic R–R intervals (RRIs) in either a time or a frequency domain is a useful tool for assessing cardiac autonomic dysfunction in clinical research. For convenience, pulse–pulse intervals (PPIs) acquired by photoplethysmography have been used to assess HRV. However, the compatibility of PPI with RRI is controversial. **Materials and Methods:** In this study, we investigated the compatibility of PPI with RRI in five groups of participants, including nonoverweight young individuals with a body mass index (BMI) <24 kg/m^2 (Group 1, n = 20, aged 18–40 years), overweight young individuals with a BMI ≥24 kg/m^2 (Group 2, n = 13, aged 21–38 years), nonoverweight upper middle-aged individuals with a BMI <24 kg/m^2 (Group 3, n = 21, aged 45–89 years), overweight upper middle-aged individuals with a BMI ≥24 kg/m^2 (Group 4, n = 14, aged 43–74 years), and diabetic patients with a BMI ≥24 kg/m^2 (Group 5, n = 19, aged 35–74 years). We then used cross-approximate entropy (CAE) to assess the compatibility between RRI and PPI and analyzed HRV in the time and frequency domains derived from PPR and RRI with traditional methods. **Results:** The CAE values in Group 1 were significantly lower than those in Group 2 (1.68 ± 0.16 vs. 1.78 ± 0.15, P = 0.041), Group 3 (1.68 ± 0.16 vs. 2.05 ± 0.27, P < 0.001), Group 4 (1.68 ± 0.16 vs. 1.87 ± 0.23, P = 0.023), and Group 5 (1.68 ± 0.16 vs. 2.09 ± 0.23, P < 0.001). There were no significant differences in HRV acquired by PPI and RRI, except for proportion of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording in Group 1. All HRVs derived from PPI were different from those acquired from RRI in the other groups. **Conclusion:** PPI may be an alternative parameter for effectively assessing cardiac autonomic function in nonoverweight healthy individuals. It should be used carefully in overweight, elderly, or diabetic individuals.

Keywords: *Cross-approximate entropy, Heart rate variability, Pulse transit time, R–R intervals*

Introduction

Heart rate variability (HRV) is the beat-to-beat oscillation modulated by sympathetic and parasympathetic nerves [1]. Decreased HRV is indicative of cardiac autonomic dysfunction, which has been associated with a grave prognosis regardless of the presence of structural heart disease [2]. Meanwhile, HRV imbalance is also known to be related to diabetic neuropathy or autonomic dysfunction [3]. HRV is primarily assessed through analysis of R–R intervals (RRIs) in electrocardiographic (ECG) recordings using a wide range of commercial devices. Common parameters used for HRV analysis are standard deviation of normal to normal (SDNN), root mean square of successive differences between adjacent normal cycles (RMSSD), and proportion of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording (pNN50) in the time domain and low-frequency power (LFP)/high-frequency power (HFP) ratio (LHR) by fast Fourier transform (FFT) in the frequency domain [4]. However, the use of ECG recordings for RRI analysis has a number of drawbacks, such as noise generated by surface electromyography, respiration-induced baseline drift, power line interference, and electrode slippage. In addition, morphological variations in ECG waveforms and heterogeneity

Access this article online
Quick Response Code:
Website: www.tcmjmed.com
DOI: 10.4103/tcmj.tcmj_68_18

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How to cite this article: Sun CK, Liu CC, Liu WM, Wu HT, Huang RM, Liu AB. Compatibility of pulse–pulse intervals with R–R intervals in assessing cardiac autonomic function and its relation to risks of atherosclerosis. Tzu Chi Med J 2020;32(1):41-6.

of the QRS complex often contribute to difficulty in the identification of R wave [5].

Photoplethysmography (PPG) is an optical technique used to monitor changes of blood volume in the microvascular bed of tissue [6]. Advances in semiconductor technology and optoelectronics have facilitated the application of PPG in clinical monitoring of the pulse rate, blood pressure, and oxygen saturation [7]. Thus, measuring the pulse–pulse interval (PPI) using PPG is another approach to the assessment of cardiac autonomic function. Compared to ECG, pulse signals can be traced using a single sensor without the need for electrodes or having the examinee undress. Therefore, PPI has previously been used as an alternative for analysis of HRV [8]. However, some researchers have suggested that pulse rate variability (PRV) derived from PPG cannot be considered a surrogate of HRV analysis [9,10]. Recently, a comprehensive review article claimed that the results of HRV analysis using PPI and RRI may differ in a short-term recording [4]. The current study examined a range of experimental parameters and methods of analysis to determine the compatibility of PPI with RRI in HRV analysis.

Cross-approximate entropy (CAE) is an improved method for analyzing two synchronous physiological signals in time series, defining the relationship between these series, and calculating the complexity within that relationship. Therefore, the CAE method can analyze dynamic changes between two series to evaluate a complex physiologic system. Specifically, similarities associated with changes in the two series can be used to observe regulatory mechanisms within a physiologic system [11,12]. In this study, the RRI and PPI were recorded using Lead II ECG and PPG on the left index finger of individuals. Similarities between the RRI and PPI were quantified according to CAE. We also analyzed the relationships among CAE and risk factors for cardiovascular disorders including age, low-density lipoprotein (LDL), cholesterol, triglycerides, fasting blood sugar, and glycosylated hemoglobin (HbA1c).

Materials and Methods

Subjects

A total of 87 individuals were recruited from Hualien Hospital, Taiwan, between July 2009 and October 2012. Among these participants, 68 were recruited from an adult health examination program and 19 diabetic patients were recruited from the diabetes clinic. According to the Bureau of Health Promotion, Ministry of Health and Welfare, Taiwan, the definition of overweight for Taiwanese is a body mass index (BMI) ≥24 kg/m^2 [13]. Thus, we divided the individuals into five groups as follows: young individuals with a BMI <24 kg/m^2 (Group 1, n = 20, aged 18–40 years), overweight young individuals with a BMI ≥24 kg/m^2 (Group 2, n = 13, aged 21–38 years), healthy upper middle-aged individuals with a BMI <24 kg/m^2 (Group 3, n = 21, aged 45–89 years), overweight upper middle-aged individuals with a BMI ≥24 kg/m^2 (Group 4, n = 14, aged 43–74 years), and diabetic patients with a BMI ≥24 kg/m^2 (Group 5, n = 19, aged 35–74 years). Diabetes was defined as an HbA1c concentration over 6.5%. All patients had to be diagnosed at our institution and followed for at least 2 months [14]. Blood tests for each individual included high-density lipoprotein (HDL), LDL, triglycerides, cholesterol, HbA1c, and fasting blood sugar. All individuals were required to fill out a questionnaire regarding their lifestyle, smoking habits, and medical history as well as refrain from caffeine-containing beverages and theophylline-containing medication for 8 h before each hospital visit. During each visit, blood pressure was obtained once over the left arm of supine individuals using an automated oscillometric device (BP 3AG1, Microlife, Taiwan) with a cuff of appropriate size. Individuals were permitted to rest in a supine position in a quiet, temperature-controlled room at 25°C ± 1°C for 5 min before data acquisition that lasted for 30 min. The first 5-min data were used for analysis in the present study.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institution (IRB 98-06-02). Informed written consent was obtained from all patients before their enrollment in this study.

Data acquisition for R–R intervals and pulse–pulse intervals

Figure 1 presents a Lead II ECG obtained using the conventional method and synchronous volume pulse acquired by an infrared PPG sensor attached to the index finger of the left hand. Following processing through an analog-to-digital converter (USB-6009 DAQ, National Instruments, Austin, TX, USA) at a sampling frequency of 500 Hz, the digitized signals were stored in a computer. The time difference between the peaks of two consecutive ECG R waves was defined as the RRI, and the time difference between the peaks of two consecutive PPG waves was defined as the PPI. We used empirical mode decomposition (EMD) to deconstruct the RRI and PPI series, thereby eliminating the trend from the original series [15].

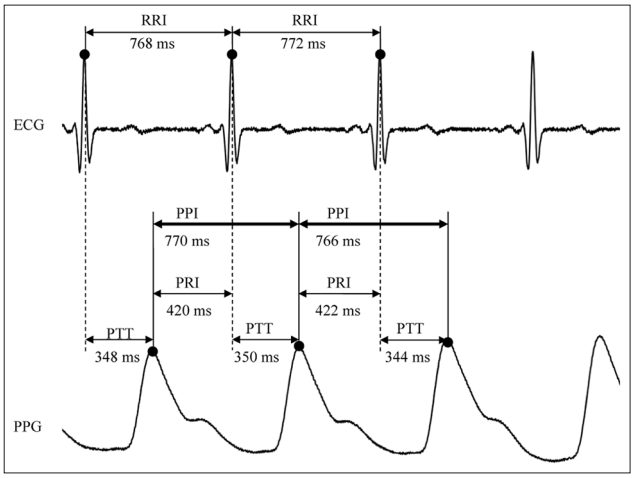

Figure 1: The definition of time periods used in this article. R–R interval: The period between two consecutive electrocardiographic R waves; pulse–pulse interval: The period between the peaks of two consecutive volume pulses; pulse transit time: The period between an electrocardiographic R wave and the peak of a succeeding pulse wave; pulse–R wave interval: The period between the peak of a pulse wave and the next electrocardiographic R wave. There are differences between the R–R intervals and corresponding pulse–pulse intervals

Analysis of heart rate variability and pulse rate variability

In this study, the time-domain measurements of HRV and PRV included SDNN, RMSSD, and pNN50 [16]. We used FFT to analyze the frequency domains of the RRI and PPI. LFP was derived in the 0.04–0.15 Hz range, while HFP was obtained in the 0.15–0.4 Hz range. In this study, the LHR of variations in the RRI and PPI was defined as the ratio of LFP to HFP [Figure 2] [17].

Compatibility of pulse–pulse intervals with R–R intervals

Compatibility of the PPI and RRI was quantified by CAE. CAE of the RRI and PPI series was adopted for the present study as we previously described [14]. The parameters for calculating CAE in this study were set at $m = 2$, $r = 0.15$, and $n = 360$.

Pulse interval analysis

As shown in Figure 1, we divided a PPI into the pulse peak–R wave interval (PRI) and pulse transit time (PTT) [18] by the time point of the ECG R wave that follows. After using EMD to eliminate the trend from the PRI and PTT series, we used approximate entropy (AE) [19] to assess the complexities of the PRI and PTT. The parameters for calculating AE in this study were set at $m = 2$, $r = 0.15$, and $n = 360$.

Statistical analysis

Average values were expressed as mean ± standard deviation. Significant differences in CAE and AE values between the two groups were determined using the nonparametric Mann–Whitney U-test. Significance in the differences between the time-domain and frequency-domain parameters in each group was determined using the paired *t*-test. The correlations between CAE values and risk factors were analyzed using the Spearman's correlation test. All statistical analyses were performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Results

Parameters for groups

Table 1 shows significant differences between Group 1 and Group 2 in terms of waist circumference (77.00 ± 4.91 cm vs. 94.08 ± 8.75 cm, $P < 0.001$), BMI (21.64 ± 1.20 kg/m^2 vs. 27.30 ± 2.48 kg/m^2, $P < 0.001$), systolic blood pressure (113.10 ± 9.51 mmHg vs. 124.77 ± 9.09 mmHg, $P = 0.001$), and triglycerides (57.35 ± 16.12 mg/dL vs. 121.69 ± 54.21 mg/dL, $P < 0.001$), whereas significant differences were noted between Group 3 and Group 4 only in waist circumference (76.64 ± 8.61 cm

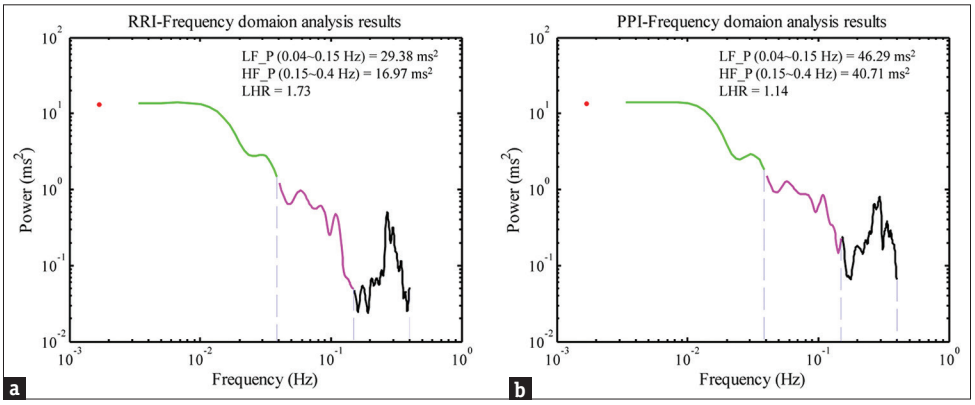

Figure 2: Spectral analysis of the R–R intervals and pulse–pulse intervals of a 76-year-old man with poorly controlled diabetes (glycosylated hemoglobin: 9.6%, Group 5). The low-frequency power/high-frequency power ratio driven from the R–R intervals (a) is different from those driven from pulse–pulse intervals (b) (1.73 vs. 1.14). The low frequency ranges from 0.04 to 0.15 Hz and high frequency ranges from 0.15 to 0.4 Hz

Table 1: Comparison of parameters in different groups

	Group 1 (*n*=20)	Group 2 (*n*=13)	Group 3 (*n*=21)	Group 4 (*n*=14)	Group 5 (*n*=19)
Age (years)	24.35±5.44	26.46±5.27	56.05±9.46	57.29±9.09	58.89±11.52
Waist circumference (cm)	77.00±4.91	94.08±8.75*	76.64±8.61	89.14±6.56†	95.95±10.05‡
SBP (mmHg)	113.10±9.51	124.77±9.09*	117.33±14.52	121.21±13.96	131.00±18.26
DBP (mmHg)	69.15±7.26	75.00±7.54	72.48±7.79	74.14±8.22	79.53±10.16
HDL (mg/dL)	45.95±9.19	41.77±10.14	57.42±21.76	53.14±14.97	39.42±9.51‡
LDL (mg/dL)	99.20±32.96	112.62±42.28	129.10±24.44	115.93±21.86	107.16±29.30
Cholesterol (mg/dL)	163.25±35.35	178.85±42.18	198.46±23.37	191.23±27.13	173.26±38.06‡
Triglycerides (mg/dL)	57.35±16.12	121.69±54.21*	94.11±43.84	108.00±18.76	138.63±69.86
Fasting blood sugar (mg/dL)	90.30±4.66	92.00±5.99	95.74±14.56	102.57±18.76	142.74±52.71‡
HbA1c (%)	5.42±0.31	5.48±0.26	5.87±0.38	5.85±0.42	7.45±1.84‡

*P<0.05 Group 1 versus Group 2, †P<0.05 Group 3 versus Group 4, ‡P<0.05 Group 4 versus Group 5. Significance of differences determined by the nonparametric 53 Mann-Whitney U-test. Data are presented as the mean±SD. Group 1: Healthy young individuals with a BMI <24 kg/m^2, Group 2: Overweight young individuals with a BMI ≥24 kg/m^2, Group 3: Healthy upper middle-aged 54 individuals with a BMI <24 kg/m^2, Group 4: Overweight upper middle-aged individuals with a BMI ≥kg/m^2, Group 5: Overweight diabetic individuals with 55 a BMI ≥24 kg/m^2. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL: High-density lipoprotein, LDL: Low-density 56 lipoprotein, HbA1c: Glycosylated hemoglobin, SD: Standard deviation

vs. 89.14 ± 6.56 cm, $P < 0.001$) and BMI (21.45 ± 1.55 kg/m^2 vs. 26.87 ± 2.51 kg/m^2, $P < 0.001$). On the other hand, there was a significantly different in waist circumference (89.14 ± 6.56 cm vs. 95.95 ± 10.05 cm, $P < 0.05$), HDL (53.14 ± 14.97 mg/dL vs. 39.42 ± 9.51 mg/dL, $P < 0.01$), cholesterol level (191.23 ± 27.13 mg/dL vs. 173.26 ± 38.06, $P < 0.05$), fasting blood sugar (102.57 ± 18.76 mg/dL vs. 138.63 ± 69.86 mg/dL, $P < 0.01$), and HbA1c level (5.85 ± 0.42% vs. 7.45 ± 1.84%, $P < 0.001$) between Group 4 and Group 5.

Comparisons of heart rate variability and pulse rate variability

As shown in Table 2, there were no significant differences between the RRI and PPI in all groups. However, the parameters of HRV were similar to those of the PRV except pNN50 by RRI and PPI (18.37% ± 18.03% vs. 20.11 ± 17.94%, $P < 0.001$) in Group 1. Table 2 also demonstrates that the parameters of HRV were different from those of PRV in both the time and frequency domains in all other groups. Meanwhile, the parameters derived from the PPI in the time domain were higher, whereas those of the frequency domain were lower, than those acquired using the RRI.

Approximate entropy values for peak–R wave interval and pulse transit time and cross-approximate entropy values for R–R intervals and pulse–pulse intervals

As shown in Table 3, the AE values of PTT in Group 1 were significantly lower than those in Group 2 (1.10 ± 0.22 vs. 1.27 ± 0.19, $P < 0.05$) but higher than those in Group 3 (1.10 ± 0.22 vs. 0.78 ± 0.36, $P < 0.01$), Group 4 (1.10 ± 0.22 vs. 0.90 ± 0.25, $P < 0.05$), and Group 5 (1.10 ± 0.22 vs. 0.82 ± 0.34, $P < 0.05$). By contrast, the AE values of the PRI were lower in Group 1 than in Groups 2, 3, 4, and 5 (0.01 ± 0.01 vs. 0.08 ± 0.08, 0.08 ± 0.11, 0.06 ± 0.10, and 0.14 ± 0.20, respectively, all $P < 0.05$).

The CAE values in Group 1 were significantly lower than those in Group 2 (1.68 ± 0.16 vs. 1.78 ± 0.15, $P < 0.05$), Group 3 (1.68 ± 0.16 vs. 2.05 ± 0.27, $P < 0.001$), Group 4 (1.68 ± 0.16 vs. 1.87 ± 0.23, $P < 0.05$), and Group 5 (1.68 ± 0.16 vs. 2.09 ± 0.23, $P < 0.001$).

Correlation between cross-approximate entropy values and risk factors

Table 4 shows that CAE values were positively correlated with age ($r = 0.574$, $P < 0.001$), diastolic blood pressure (DBP) ($r = 0.222$, $P = 0.039$), LDL ($r = 0.263$, $P = 0.015$), cholesterol ($r = 0.264$, $P = 0.020$), triglycerides ($r = 0.387$, $P < 0.001$), fasting blood sugar ($r = 0.384$, $P < 0.001$), and HbA1c ($r = 0.562$, $P < 0.001$).

Discussion

Changes in HRV can be found in patients with autonomic dysfunction. Decreased HRV also indicates a grave prognosis in patients with stroke and congestive heart failure. However, the compatibility of PPI with RRI in analysis of HRV is controversial. Relevant literature focusing on this topic is limited. In concert with the results of previous studies using young individuals [20,21], the present study

Table 2: Comparison of heart rate variability and pulse rate variability in time and frequency in each group

Parameters	Group 1		Group 2		Group 3		Group 4		Group 5	
	HRV	PRV	HRV	PRV	HRV	PRV	HRV	PRV	HRV	PRV
BBI (m)	897.15±135.89	897.28±135.93	781.90±124.25	781.92±124.24	931.90±133.01	931.86±132.98	889.83±89.55	889.84±89.60	838.42±105.51	838.51±104.66
SDNN (m)	49.88±16.19	49.75±15.51	35.65±17.89	36.55±17.99†	31.89±9.51	35.72±10.62‡	34.79±15.21	37.81±14.02#	25.87±15.47	29.37±15.34¶
RMSSD (m)	42.68±24.05	41.45±20.24	24.30±14.89	26.15±15.04†	23.01±8.22	34.20±15.87‡	22.39±8.28	31.08±11.20#	22.06±16.10	32.01±16.56¶
pNN50 (%)	18.37±18.03	20.11±17.94*	7.10±14.74	7.95±15.17†	4.25±5.40	13.42±13.24‡	3.57±6.88	7.64±8.51#	6.88±13.35	12.68±14.82¶
LHR	1.55±0.79	1.51±0.72	2.09±1.14	1.84±0.93†	1.40±0.73	1.10±0.63‡	1.94±1.48	1.43±0.94#	1.24±0.89	0.78±0.60¶

*$P<0.05$ HRV versus PRV in Group 1, †$P<0.05$ HRV versus PRV in Group 2, ‡$P<0.05$ HRV versus PRV in Group 3, #$P<0.05$ HRV versus PRV in Group 4, ¶$P<0.05$ HRV versus PRV in Group 5. Significance of differences determined by the nonparametric Mann-Whitney U-test. Values are expressed as mean±SD. Group 1: Healthy young individuals with a BMI <24 kg/m^2, Group 2: Overweight young individuals with a BMI ≥24 kg/m^2, Group 3: Healthy upper middle-aged individuals with a BMI <24 kg/m^2, Group 4: Overweight upper middle-aged individuals with a BMI ≥24 kg/m^2, Group 5: Overweight diabetic individuals with a BMI ≥24 kg/m^2. BBI: Beat-beat intervals, SDNN: Standard deviation of normal to normal, RMSSD: Root mean square of successive differences between adjacent normal cycles, pNN50: Proportion of pairs of adjacent NN intervals differing by >50 m in the entire recording, LHR: Low-frequency power/high-frequency power ratio, RRI: R-R intervals, PPI: Pulse-pulse intervals, HRV: Heart rate variability, PRV: Pulse rate variability, SD: Standard deviation, BMI: Body mass index

Table 3: Comparison of cross-approximate entropy values and approximate entropy values in different groups

	Group 1 (*n*=20)	Group 2 (*n*=13)	Group 3 (*n*=21)	Group 4 (*n*=14)	Group 5 (*n*=19)
AE (PRI)	0.01±0.01	0.08±0.08*	0.08±0.11†	0.06±0.10‡	0.14±0.20¶
AE (PTT)	1.10±0.22	1.27±0.19*	0.78±0.36†	0.90±0.25‡	0.82±0.34¶
CAE (RRI, PPI)	1.68±0.16	1.78±0.15*	2.05±0.27†	1.87±0.23‡	2.09±0.23¶

*P<0.05 Group 1 versus Group 2, †P<0.05 Group 3 versus Group 1, ‡P<0.05 Group 4 versus Group 1, ¶P<0.05 Group 5 versus Group 1. Significance of differences determined by the nonparametric Mann-Whitney U-test. Data are presented as the mean±SD. Group 1: Healthy young individuals with a BMI <24 kg/m^2, Group 2: Overweight healthy young individuals with a BMI ≥24 kg/m^2, Group 3: Healthy upper middle-aged individuals with a BMI <24 kg/m^2, Group 4: Overweight healthy upper middle-aged individuals with BMI ≥24 kg/m^2, Group 5: Overweight type 2 diabetic patients with a BMI ≥24 kg/m^2. CAE (RRI, PPI): Cross-approximate entropy of the R-R interval and pulse-pulse interval, AE (PRI): Approximate entropy of the pulse peak-R wave interval, AE (PTT): Approximate entropy of the pulse transit time, BMI: Body mass index, SD: Standard deviation

Table 4: Correlations between cross-approximate entropy values and risk factors

	CAE value (*r*, *P*)
Age (years)	0.574, <0.001
DBP (mmHg)	0.222, 0.039
LDL (mg/dL)	0.263, 0.015
Cholesterol (mg/dL)	0.264, 0.020
Triglyceride (mg/dL)	0.387, <0.001
Fasting blood sugar (mg/dL)	0.384, <0.001
HbA1c (%)	0.562, <0.001

Significance of differences determined by the Spearman's correlation test. DBP: Diastolic blood pressure, LDL: Low-density lipoprotein, HbA1c: Glycosylated hemoglobin, CAE value: Cross-approximate entropy value between R-R intervals and pulse-pulse intervals

also demonstrated a high degree of agreement between HRV and PRV in both time and frequency domains in Group 1. However, significant differences between HRV and PRV in elderly individuals have been reported previously [10], similar to our results. To check the compatibility of PPI with RRI in depth, we stratified our sampled individuals into five groups as shown in Table 1.

In our study, the HRV was different from PRV in both the time and frequency domains in Groups 2–5. It seems that the parameters derived from the PPI in the time domain, including the SDNN, RMSSD, and pNN50, tended to be larger, whereas the index in the frequency domain (i.e., LHR) tended to be smaller, than those acquired using RRI [Table 2]. This point should be taken into account in the clinical application of PPG pulse signals in the assessment of cardiac autonomic function. Consistent with the results of previous studies [22,23], our study disclosed that the LHR was decreased in the elderly and diabetic patients (comparisons between Groups 1 and 3, 5). Interestingly, the LHR was increased in both young and elderly overweight healthy individuals (Group 1 vs. Group 2 and Group 3 vs. Group 4) in the current study. Similar results were obtained in previous studies in which obese individuals were found to exhibit higher HRV than that nonobese individuals [24,25]. Nevertheless, this trend was not observed in children [26].

CAE indicates the compatibility of two series of data. Table 3 demonstrates that the CAE values of the PPI and RRI were increased in the overweight, elderly, and diabetic individuals, and HRV values derived from the PPI and RRI were different in the time and frequency domains. Because of the small sample size, we could not identify a cutoff CAE value. Further study with a larger sample size may be helpful in defining a cutoff point for CAE which will be beneficial for improving the accuracy of clinical measurements of cardiac autonomic nerve function. Furthermore, Table 4 shows that the CAE values increased with increasing age, DBP, LDL, cholesterol, triglycerides, fasting blood sugar, and HbA1c. The above findings suggest that the risk factors of atherosclerosis influence the compatibility of PPI with RRI.

As shown in Figure 1, PPIs are not similar to RRIs (770 ms, 766 ms vs. 768 ms, 772 ms). Interestingly, the mean values of the PPI and RRI were the same in all the groups [Table 2]. To check the determining factors influencing the compatibility of PPI with RRI, we divided the PPI into the PRI and the PTT by the time point of the following ECG R wave [Figure 1]. While the AE value of the PTT was reduced, the AE value of the PRI was increased in elderly and diabetic individuals and correlated with the CAE values of the RRI and PPI [Table 3]. Therefore, the complexity of the PRI should be the determining factor influencing the compatibility between the PPI and RRI. Further studies, however, are required to establish the physiological and clinical significance of this parameter.

Conclusion

Although the present study showed that PRV could be applicable as an alternative means of evaluating cardiac autonomic function in healthy young individuals with normal BMIs, it appears inappropriate for overweight, elderly, and diabetic individuals. Therefore, discretion should be taken when evaluating autonomic nerve function such as HRV or baroreflex activity with the PPI.

Financial support and sponsorship

This work was partly supported by a grant from the Ministry of Science and Technology (MOST 103-2221-E-303-002).

Conflicts of interest

There are no conflicts of interest.

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