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Assessing Spontaneous Baroreflex in Aged with Pulse-Pulse Intervals and Pulse Amplitudes

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***Abstract*—Cardiac autonomic dysfunction is a serious condition in the elder subjects. Baroreflex sensitivity (BRS) by measuring pulse intervals and blood pressure has been proven as an effective indicator. This paper proposes a novel index by substitution blood pressure with amplitudes of pressure pulse. We recruited 61 subjects divided into two groups: healthy young subjects (Group1, n=33), healthy elders (Group2, n=28). The wrist pulse pressures of each subject were measured for 5 minutes to obtain pulse-pulse intervals and amplitudes then applied within the spontaneous sequence technique to calculate the pulse-pulse interval and amplitude ratio (PAR). We verified the reproducibility of PAR and agreement with spectral analysis of heart rate variability in group1 participants. We discovered significant differences between different groups in PAR (Group1 *vs*. Group2: 0.90±0.42 *vs*. 0.62±0.27, *P*=0.010). In contrast with measurements of BRS, this study proposes a simple approach without the necessity of blood pressure calibration or professional expertise to conduct measurements, thereby providing a convenient method for assessing autonomic function at home.**

I. Introduction

Arterial baroreflex plays a key role in the homeostasis of blood pressure. It provides a negative feedback loop from the baroreceptors in the aortic arch and carotid sinuses to the nucleus of the solitary tract in the brainstem through the glosopharyngeal and vagus nerves. Elevated blood pressure stimulates the baroreceptors to increase parasympathetic activity, which slows the heart rate, decreases cardiac contractility, and causes vasodilatation [1]. Based on this physiological phenomenon, baroreflex sensitivity (BRS) has been used as an index of autonomic innervation of the heart. BRS is quantified as the slope of the relationship between the increment of systolic blood pressure (SBP) and the lengthening of inter-beat intervals of the heart following an intravenous injection of phenylephrine [2]. BRS has been shown to decrease with age, the presence of hypertension, and various cardiovascular diseases [3, 4]. The development of techniques allowing noninvasive beat-to-beat measurement of blood pressure has expanded the application of BRS in clinical research. BRS has been defined as the slope of the relationship between spontaneous changes in SBP and pulse-pulse intervals (PPI) by the spontaneous sequence method [5, 6]. A decrease in BRS has been linked to many diseases and may be used as a prognostic indicator of myocardial infarction [7-12].

At present, the time domain assessment of BRS involves determining the slope of the relationship between spontaneous oscillations in blood pressure and pulse-pulse intervals using commercially available machines such as Finapres 2300 or Finometer Pro ® or Portapres. These machines are expensive and require calibration prior to each measurement. It has been shown that the amplitude of pulse pressure in the radial artery is strongly correlated with systemic blood pressure. The waveform of radial pulse can be used to estimate blood pressure in the ascending aorta [13, 14]. We previously proposed an instrument to assess endothelial function and arterial stiffness by analyzing pressure pulse in the radial artery [15, 16]. In this study, we propose a new method to assess cardiovascular autonomic function in aged and diabetic subjects using the spontaneous sequence technique to estimate the relationship between the normalized amplitudes of pressure pulse and pulse-pulse intervals (PPI) acquired from the radial artery. The usefulness of this new parameter, pulse-pulse interval and amplitude ratio (PAR), was compared with analysis of the frequency domain of HRV using fast Fourier transform (FFT).

II. Materials and Methods

A. Subjects

This study recruited 61 subjects from Hualien Hospital, Taiwan between July, 2009, and October, 2012. Among these subjects were recruited from adult health examinations. The blood tests administered to each subject including glycosylated hemoglobin (HbA1c), fasting blood sugar, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and cholesterol. 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.

These subjects were then divided into two groups: healthy young subjects (Group1, age range: 20 - 40, n = 33), healthy upper middle-aged subjects (Group2, age range: 41 - 70, n = 28). All healthy subjects had no personal or family history of cardiovascular disease. 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

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arm of the supine subjects using an automated oscillometric device (BP3AG1, Microlife, Taiwan) with a cuff of appropriate size.

B. Extraction of Wrist Pulse Signal

Using a pressure sensor (FGN-607PGSR, Fujikura, Japan), we applied a constant pressure of 40 mmHg at the wrist cuff to obtain pressure signals from the radial artery [15, 16]. Pulse signals were recorded for consecutive 5 minutes for PAR calculation.

The PPI series and amplitude series employed in this study are shown in Fig.1. Using half of the maximal value during the five-minute measurement as the low threshold, we applied the first derivative equal to zero as the local maximum of each pulse signal, which we regarded as the peak of each pulse wave. PPI is the time interval between two adjacent peaks; therefore, the PPI series is {*PPI*(1), *PPI*(2), *PPI*(3), …, *PPI*(*n*)}.The valley was defined as the minimum between two adjacent peeks. We defined a single amplitude as the potential difference between the peak and the valley prior to it, such that successive amplitudes form an amplitude series, which is {*Amplitude* (1), *Amplitude* (2), *Amplitude* (3), …, *Amplitude* (*n*)}.

C. Calculation of PAR Using Wrist Pulse Signals

We applied the spontaneous sequence technique [5, 6], previously used to calculate BRS, to the wrist pulse signals, thereby normalizing the PPIs and amplitudes of the entire section. PPI and amplitude series with three consecutive increases after normalization were recorded before calculating the linear relationships and slopes between the PPI and amplitude of each series. Only slopes with correlation coefficients greater than 0.9 were used [17]. Subsequently, the mean of all the slopes served as the PAR. The entire calculation process in exhibited in Fig.2.

D. The Reproducibility of PAR in Three Consecutive Measurements

Ten of the healthy, young subjects in Group1 agreed to perform measurements at the same time on three consecutive days. They refrained from drinking caffeinated beverages 8 hours before measurements. Prior to measurement, the subjects rested in a supine position for 5 minutes in a quiet environment at 25 °C. We calculated the technical error of measurement (TEM) to evaluate the reproducibility of measurement results from three consecutive days [18].

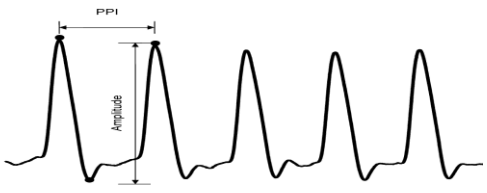

Figure 1. Wrist pulse signal

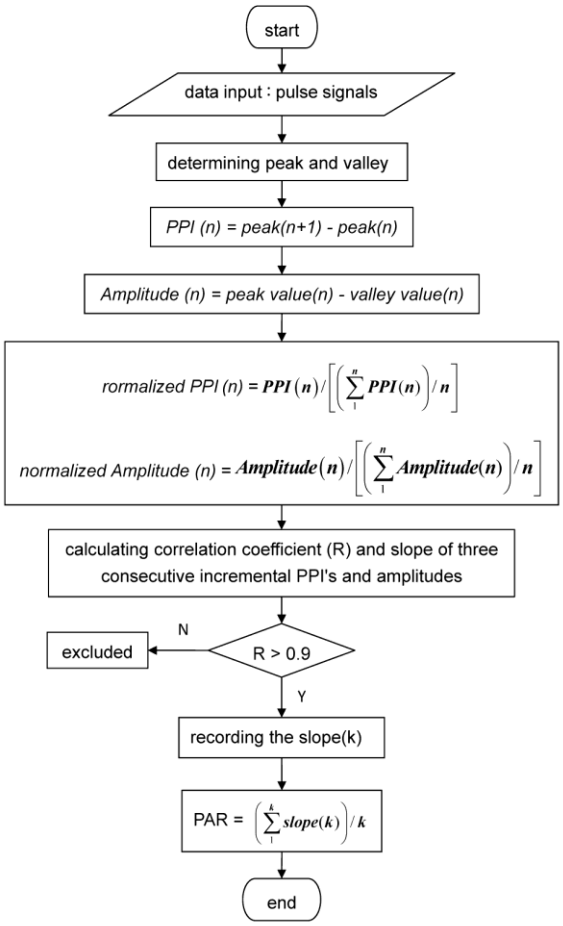

Figure 2. Calculation process for PAR

E. Fast Fourier Transform of Heart Rate Variability

Variation of PPI was quantified by fast Fourier transform as used for frequency domain analysis of RRI [19]. 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. In this study, the LFP/HFP ratio (LHR) of PPI variation serves as an indicator of autonomic function.

F. Statistical Analysis

Average values were expressed as mean ± SD. We used the technique error of measurement (TEM) to examine the reproducibility of measurements. Significant agreement between parameters and measurements was noted using Bland-Altman analysis. The significance of difference in anthropometric, hemodynamic, and computational parameters between different groups was determined using the Mann-Whitney *U* test. The correlation between PAR and risk factors for different groups was compared 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

We first employed TEM to evaluate the reproducibility of PAR using the measurements from 10 healthy, young subjects on three consecutive days. Next, we compared the physiological indices, blood parameters, and PAR from healthy young subjects (Group1), healthy upper middle-aged subjects (Group2).

A. The Reproducibility and Reliability of PAR

As shown in Table I, the TEM value derived from the 10 young subjects on three consecutive days equals 0.0472, which is less than 0.05. As a result, the PAR derived from three measurements is reproducible.

Fig.3 presents the 30 PAR indicators derived from the measurements of ten healthy, young subjects on three consecutive days. An assessment of PAR and LHR showed good agreement between the two indicators.

TABLE I. USE OF TECHNICAL ERROR OF MEASUREMENT TO EVALUATE REPRODUCIBILITY OF PAR ASSESSED ON THREE CONSECUTIVE DAYS FROM TEN HEALTHY, YOUNG SUBJECTS

	The number of measurement			**(1)**	**(2)**	
	1	***2***	***3***	ΣM^2	$(\Sigma M)^2/K$	***(1) - (2)***
Subject no.						
1	0.7975	0.7737	0.8949	2.0355	2.0272	0.0083
2	0.2912	0.3054	0.3346	0.2782	0.2768	0.0014
3	0.7903	0.7780	0.8435	1.9414	1.9389	0.0025
4	0.8129	0.7913	0.9062	2.1082	2.1007	0.0075
5	0.1541	0.1425	0.1033	0.0547	0.0533	0.0014
6	0.4708	0.4758	0.5661	0.7685	0.7628	0.0057
7	0.7874	0.6927	0.6598	1.5352	1.5264	0.0088
8	0.6138	0.6802	0.6381	1.2466	1.2443	0.0023
9	0.2832	0.3426	0.2577	0.2640	0.2602	0.0038
10	0.3059	0.3789	0.3305	0.3464	0.3236	0.0028
$TEM = \sqrt{\Sigma((1)-(2))/(N(K-1))} = \sqrt{0.0472/(10\ (3-1))} = 0.0472$						$\Sigma =$ 0.0472

M: measured values; K: number of measurement; N: number of subjects.

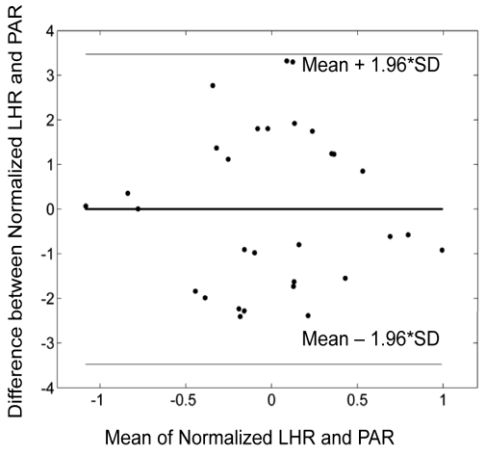

Figure 3. Bland-Altman plot of pulse-pulse interval and amplitude ratio (PAR) and low frequency power/high frequency power ratio (LHR) assessed on three consecutive days from ten healthy, young subjects

B. Comparison of Anthropometric, Hemodynamic, and Computational Parameters Between Healthy Young Subjects (Group1) and Healthy Upper Middle-Aged Subjects (Group2)

Table II displays significant differences between Group1 and Group2 in terms of age (27.24 ± 5.94 years vs. 55.36 ± 6.15 years, $P < 0.001$) and body height (1.70 ± 0.08 m vs. 1.62 ± 0.08 m, $P < 0.001$). Their blood samples also presented significant differences in triglyceride (82.15 ± 55.25 mg/dL vs. 101.15 ± 51.41 mg/dL, $P = 0.045$) and HbA1c (5.49 ± 0.27 % vs. 5.79 ± 0.35%, $P < 0.001$), but not in fasting blood sugar (91.70 ± 6.36 mg/dL vs.93.90 ± 15.35 mg/dL, $P = 0.22$). Significant differences did not exist between the two groups in LHR (1.51 ± 1.39 vs. 1.04 ± 0.75, $P = 0.253$). The PAR values in Group1 were significantly higher than those in Group2 (0.90 ± 0.42 vs. 0.62 ± 0.27, $P = 0.010$).

IV. DISCUSSION

Initially, the assessment of BRS required invasive methods to measure continuous changes in blood pressure; catheters were inserted into the aorta to measure blood pressure and changes in the blood pressure were recorded after the injection of drugs. BRS was then calculated using the RRI series from ECGs [2]. Invasive methods inflict harm on subjects and must be performed by trained professionals. As a result, they are unsuitable for clinical research. Recently, researchers have used devices such as Finapres 2300, Finometer Pro®, and Portapres, which convert PPG signals from the finger to blood pressure, to monitor beat-to-beat blood pressure, thereby generalizing the use of BRS in clinical research. However, these instruments are costly and require time for calibration before measurements. Due to the positive correlation between blood pressure and pulse wave amplitudes, we substituted the amplitude of pressure pulse acquired by our instruments at the wrist for blood pressure to assess baroreflex activity in this study. We then evaluated this approach by performing measurements on healthy young subjects over three consecutive days. Table I shows the high reproducibility of PAR in healthy young individuals (TEM = 0.0472) as well as the strong agreement between PAR and LHR, which is conventionally used to assess autonomic function (Fig.3). This demonstrates the feasibility of using PAR as an index. This noninvasive method of measurement reduces time consumption in blood pressure conversion and calibration, providing convenience and the possibility to perform measurements at home.

The PAR comparisons between healthy young subjects (Group1) and healthy upper middle-aged subjects (Group2) in Table II (Group1 *vs*.Group2: 0.90 ± 0.42 *vs*. 0.62 ± 0.27, $P = 0.010$). Although LHR decreased with age [20], we were unable to derive significant differences in LHR in this study. We speculate that this may be a result of the small sample population or changes of these two parameters are caused by different pathogenesis [21]. PAR was also associated with risk factors of cardiac autonomic dysfunctions including age and glycosylated hemoglobin inversely. This supports the findings of previous research on the relationships between BRS and diabetes and between BRS and age [3].

TABLE II. COMPARISON OF PHYSIOLOGICAL PARAMETERS, BLOOD SAMPLES, HRV INDICES, AND PAR BETWEEN HEALTHY YOUNG SUBJECTS AND HEALTHY UPPER MIDDLE-AGED SUBJECTS

	Group1 (n = 33)	Group2 (n = 28)	*P value*
Age (years)	27.24 ± 5.94	55.36 ± 6.15	< 0.001
Body height (m)	1.70 ± 0.08	1.62 ± 0.08	< 0.001
Body weight (kg)	66.96 ± 12.58	65.23 ± 10.71	0.496
Waist circumference (cm)	80.88 ± 10.46	83.46 ± 11.29	0.268
BMI (kg/m^2)	22.92 ± 3.35	24.69 ± 3.24	0.058
SBP (mmHg)	118.76 ± 10.94	117.75 ± 14.04	0.822
DBP (mmHg)	72.21 ± 7.66	75.39 ± 10.12	0.255
HbA1c (%)	5.49 ± 0.27	5.79 ± 0.35	< 0.001
HDL (mg/dL)	50.85 ± 18.99	56.33 ± 37.36	0.739
LDL (mg/dL)	115.09 ± 31.70	114.67 ± 31.36	0.633
Cholesterol (mg/dL)	189.58 ± 34.73	188.05 ± 51.31	0.592
Triglyceride (mg/dL)	82.15 ± 55.25	101.15 ± 51.41	0.045
Fasting blood sugar (mg/dL)	91.70 ± 6.36	93.90 ± 15.35	0.220
LHR	1.51 ± 1.39	1.04 ± 0.75	0.253
PAR	0.90 ± 0.42	0.62 ± 0.27	0.010

Group1: healthy young subjects; Group2: healthy upper middle-aged subjects. Value are expressed as mean ± SD. SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low- density lipoprotein; LHR = low frequency power/ high frequency power ratio; PAR = pulse-pulse interval and amplitude ratio.

V. CONCLUSIONS

This study used the spontaneous sequence technique to analyze PAR derived from the correlation between wrist pulse amplitude and PPI. This could serve as a new indicator to evaluate autonomic function without the need for calibration, thereby providing a simpler method of measurement. Incorporating PAR into the previously mentioned instruments would also enable the measurement of endothelial function, the arterial stiffness index, and autonomic function.

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