Assess Spontaneous Baroreflex in Diabetic Subjects and Aged Persons Using Pressure Pulse Analysis

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Received 13 May 2013; Accepted 7 Jul 2013; doi: 10.5405/jmbe.1543

Abstract

Cardiac autonomic dysfunction is a serious condition in elderly and diabetic subjects. Baroreflex sensitivity (BRS), measured from pulse intervals and blood pressure, has been proven as an effective indicator. This paper proposes an index that replaces blood pressure with amplitudes of the pressure pulse. 89 subjects were recruited and divided into three groups: healthy young subjects (Group 1, n = 33), healthy elders (Group 2, n = 28), and type-2 diabetic patients (Group 3, n = 28). The wrist pulse pressures of each subject were measured for 5 min to obtain pulse-pulse intervals and amplitudes. The spontaneous sequence technique was then used to calculate the pulse-pulse interval to amplitude ratio (PAR). The reproducibility of the PAR and agreement with spectral analysis of heart rate variability in Group 1 participants were verified. Significant differences between different groups in the PAR (Group 1 vs. Group 2: 0.79 ± 0.40 vs. 0.54 ± 0.23, P = 0.032; Group 2 vs. Group 3: 0.54 ± 0.23 vs. 0.47 ± 0.26, P = 0.009) and a negative linear relationship between the PAR and risk factors of autonomic dysfunction were found. The proposed index does not require blood pressure calibration or professional expertise for conducting measurements, making it convenient for assessing autonomic function at home.

Keywords: Baroreflex, Autonomic function, Diabetic, Spontaneous sequence technique, Pulse-pulse interval

1. 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 vasodilation [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) determined using 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].

Type-2 diabetes mellitus has reached epidemic proportions in developed countries and associated cardiovascular, renal, and neural complications are major contributors to the increased morbidity and mortality rates in this patient population [13]. One of the most overlooked and serious complications of diabetes is autonomic neuropathy, particularly parasympathetic innervation associated with cardiovascular autonomic dysfunction, which can lead to abnormalities in the control of heart rate and the homeostasis of blood pressure [14]. Early detection of subclinical autonomic dysfunction to prevent associated complications has recently been recommended in addition to augmenting the control of blood sugar [15,16]. Several standard tests can be used to measure cardiovascular autonomic function by measuring changes in heart rate during deep breathing, while changing position, or in the Valsalva...
maneuver known as the “Ewing battery” [17]. These tests have been applied in clinical research for 30 years. The frequency domain analysis of heart rate variability (HRV) is another popular method of detecting autonomic dysfunction [18]. It should be noted that abnormal BRS has been observed in diabetic patients with normal conventional tests of autonomic function [19]. Impaired BRS may also be used as a predictor of sudden death in diabetic patients [20].

At present, the time domain assessment of BRS involves determining the slope of the relationship between spontaneous oscillations in blood pressure and PPIs using commercially available machines such as Finapres 2300, 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 systolic blood pressure (SBP) SBP. The waveform of radial pulse can be used to estimate blood pressure in the ascending aorta [21,22]. We previously proposed an instrument for assessing endothelial function and arterial stiffness that analyzes the pressure pulse in the radial artery [23,24]. In this study, a method for assessing cardiovascular autonomic function in aged and diabetic subjects that uses the spontaneous sequence technique to estimate the relationship between the normalized amplitudes of pressure pulse and PPIs acquired from the radial artery is proposed. The usefulness of the proposed parameter, PPI to amplitude ratio (PAR), was compared with analysis of the frequency domain of HRV using the fast Fourier transform (FFT).

2. Materials and methods

2.1 Subjects

This study recruited 89 subjects from Hualien Hospital, Taiwan, between July, 2009, and October, 2012. Among these subjects, the 28 diabetes patients were recruited from the diabetes clinic and the 61 healthy subjects were recruited from adult health examinations. The blood tests administered to each subject were those for 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.

The 89 subjects were then divided into three groups: healthy young subjects (Group 1, age range: 20-40 years, n = 33), healthy upper middle-aged subjects (Group 2, age range: 41-70 years, n = 28), and type-2 diabetic patients (Group 3, age range: 41-70 years, n = 28). Patients with diabetes mellitus were defined as those with glycylated hemoglobin (HbA1c) > 6.5 % or fasting blood sugar > 126 mg/dL [25] and/or having received treatment of diabetes for more than two years. All healthy subjects had no personal or family history of cardiovascular disease. The study was approved by the Institutional Review Board of Hualien Hospital. All subjects refrained from caffeine-containing beverages and theophylline-containing medication for eight hours prior to each hospital visit. Blood pressure was obtained once over the left arm of the supine subjects using an automated oscillometric device (BP3AG1, Microlife, Taiwan) with a cuff of appropriate size.

2.2 Extraction of wrist pulse signal

Using a pressure sensor (MPS-3117, Metrodyne Microsystem Corp., Hsin-Chu, Taiwan), a constant pressure of 40 mmHg was applied at the wrist cuff to obtain pressure signals from the radial artery [23,24]. The instrument is composed of a portable interception device, which consists of an air pressure sensing unit, a radius air pump motor, and a mixed-signal processing unit. The radial artery was under a stable pressure and the air pressure sensing device extracted the radial pulse waveform. A lead II electrocardiogram (ECG) was acquired simultaneously using the interception device. The notch filter for the ECG signal was set at 59-61 Hz, and the band-pass frequency was between 0.98 and 19.4 Hz. An analog-signal processing unit was used to convert the pulse wave into a direct current, filter noise, and then amplify the signal. The purified analog signal was converted into digital data using the mixed-signal processing unit (MSP430F449) with a sampling rate of 500 Hz. Then, the digital data were transmitted to a personal computer for analysis via UART (RS-232). The digital signals were stored in a high-capacity memory unit to form a pulse wave. According to previous studies on assessing HRV and BRS, 5-min measurements were obtained for each participant [26,27].

The PPI series and amplitude series employed in this study are shown in Fig. 1. Using half of the maximal value during the 5-min measurement as the low threshold, the first derivative was set equal to zero as the local maximum of each pulse signal, which was 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 peaks. A single amplitude was defined as the potential difference between the peak and the valley prior to it, such that successive amplitudes form an amplitude series, {Amplitude (1), Amplitude (2), Amplitude (3), ..., Amplitude (N)}.

![Wrist pulse signal](image)

Figure 1. Wrist pulse signal.

2.3 Calculation of PAR using wrist pulse signals

The spontaneous sequence technique [5,6], previously used to calculate BRS, was applied to the wrist pulse signals. According to the definition of peak and amplitude, the PPI
series \( \{ \text{PPI} (i) \} = \{ \text{PPI} (1), \text{PPI} (2), \text{PPI} (3), \ldots, \text{PPI} (N) \} \) and the amplitude series \( \{ \text{Amp} (i) \} = \{ \text{Amp} (1), \text{Amp} (2), \text{Amp} (3), \ldots, \text{Amp} (N) \} \) were obtained for each subject (Fig. 1). In order to reduce the effects of counterpressure at different levels of blood pressure and systemic interference, the \( \{ \text{Amp} (i) \} \) series were normalized as:

\[
\{ \text{Amp}' (i) \} = \frac{\{ \text{Amp} (i) \}}{N} \sum_{j=1}^{N} \text{Amp} (j), i = 1, 2, \ldots, N
\]  

(1)

If \( n \) sets of three consecutive rising \( \text{PPI} (i) \) and \( \text{Amp} (i) \) data points are assumed to be found from \( \{ \text{PPI} (i) \} \) and \( \{ \text{Amp} (i) \} \), then each set is defined as \( \{ \text{PPI} (k) \} \) and \( \{ \text{Amp} (k) \} \), \( k = 1, 2, 3 \). The means of \( \{ \text{PPI} (k) \} \) and \( \{ \text{Amp} (k) \} \) are defined as \( \overline{\text{PPI}}(k) \) and \( \overline{\text{Amp}}(k) \), and their standard deviations (SDs) are \( s_{\text{PPI}(k)} \) and \( s_{\text{Amp}(k)} \), respectively. The covariance of \( \{ \text{PPI} (k) \} \) and \( \{ \text{Amp} (k) \} \) is:

\[
\text{cov}\left( \{ \text{PPI} (k) \}, \{ \text{Amp} (k) \} \right) = \frac{1}{n-1} \sum_{i=1}^{n} \left[ \text{PPI} (k) - \overline{\text{PPI}}(k) \right] \left[ \text{Amp} (k) - \overline{\text{Amp}}(k) \right]
\]  

(2)

The correlation coefficient of \( \{ \text{PPI} (k) \} \) and \( \{ \text{Amp} (k) \} \), \( R \), is defined as:

\[
R = \frac{\text{cov}\left( \{ \text{PPI} (k) \}, \{ \text{Amp} (k) \} \right)}{s_{\text{PPI}(k)} \times s_{\text{Amp}(k)}}
\]  

(3)

The \( R \) value of each set is calculated using Eqs. (2) and (3) \( (n \) times), and the slope of each set is obtained using the least squares method. Assuming that there are \( b \) sets in which the \( R \) value is larger than 0.9 [28], the mean of all the slopes is PAR.

\[
\text{PAR} = \frac{1}{b} \sum_{i=1}^{b} \text{slope}(m)
\]  

(4)

2.4 Substituting PPI for R-R interval in assessing baroreflex activity

To assess the agreement of the PPI and the R-R interval (RRI), a pressure sensor was used to obtain the pulse signals of 10 healthy, young subjects at the wrist. The extracted PPIs were compared with the RRRs from the lead II ECG. The Bland-Altman method was used to measure the agreement between the two intervals [29]. Moreover, the RRI was used to substitute the PPI to calculate spontaneous baroreflex activity in terms of the R-R interval to amplitude ratio (RAR). The Bland-Altman plot was used to assess the agreement between the two parameters.

2.5 Reproducibility of PAR in three consecutive measurements

Ten of the healthy, young subjects in Group 1 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 min in a quiet environment at 25 °C. Then, linear regression was used to assess the correlation between each pair of measurements.

2.6 Fast Fourier transform of heart rate variability

HRV was quantified by FFT using the frequency domain analysis of RRI [30]. Low-frequency power (LFP) was derived in the 0.04-0.15 Hz range and high-frequency power (HFP) was derived in the 0.15-0.4 Hz range. In this study, the LFP/HFP ratio (LHR) of PPI variation served as an indicator of autonomic function.

2.7 Statistical analysis

Average values were expressed as means ± SDs. Significant agreements between PPI and RRI were determined using the correlation coefficient and those between the PAR and the RAR were determined using Bland-Altman analysis. The significance of the differences in anthropometric, hemodynamic, and computational parameters between different groups was determined using the Mann-Whitney U test. The correlation between the 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 Sciences (SPSS, version 14.0 for Windows; SPSS Inc. Chicago, IL). A \( P \) value of < 0.05 was considered statistically significant.

3. Results

The agreement between the PPI and the RRI was first verified using the correlation coefficient. Bland-Altman plots were then used to assess the agreement between the PAR and the RAR using the Bland-Altman method. Linear regression was then used to evaluate the reproducibility of each pair of measurements of the PAR from 10 healthy, young subjects on three consecutive days. Next, the physiological indices, blood biochemical parameters, and the PAR from healthy, young subjects (Group 1), healthy, upper middle-aged subjects (Group 2), and type-2 diabetic patients (Group 3) were compared. Finally, the correlation between risk factors and the PAR was determined.

3.1 Reproducibility and reliability of PAR

3.1.1 Agreement between PPI and RRI and between PAR and RAR

Figure 2 shows the correlation between PPI and RRI in one healthy young subject \( (R = 0.995, \ P < 0.001) \). The correlation coefficient of RRI and PPI demonstrates that they show high agreement \( (R \) ranged from 0.930 to 0.995, all \( P < 0.001) \) in ten healthy young subjects. In the assessment of spontaneous baroreflex activity, the calculated results of the RAR showed a high agreement with the PAR (Fig. 3).

3.1.2 Reproducibility of PAR

Figure 4 shows good correlation between the first and second measurements of the PAR in ten healthy young subjects \( (R = 0.976, \ P < 0.001) \). The correlation coefficient between measurements 2 and 3 and that between measurements 1 and 3 are 0.988 and 0.952, respectively. The coefficient of variation of two random measurements is 5.74%.
3.1.3 Reliability of PAR in young subjects

Figure 5 presents the 30 PAR indicators derived from the measurements of ten healthy, young subjects on three consecutive days. An assessment of the PAR and the LHR showed good agreement between the two indicators.

3.2 Usefulness of PAR

3.2.1 Comparison of anthropometric, hemodynamic, and computational parameters between healthy young subjects (Group 1) and healthy upper middle-aged subjects (Group 2)

Table 1 shows significant differences between Group 1 and Group 2 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. 102.33 ± 51.33 mg/dL, \( P = 0.034 \)) 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. 96.07 ± 10.34 mg/dL, \( P = 0.133 \)). Significant differences did not exist between the two groups in the LHR (1.51 ± 1.39 vs. 1.04 ± 0.75, \( P = 0.253 \)).

The PAR values in Group 1 were significantly higher than those in Group 2 (0.79 ± 0.40 vs. 0.54 ± 0.23, \( P = 0.032 \)).

Table 1. Comparison of physiological parameters, blood samples, HRV indices, and PAR between healthy young subjects and healthy upper middle-aged subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 33)</th>
<th>Group 2 (n = 28)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.24 ± 5.94</td>
<td>55.36 ± 6.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body height (m)</td>
<td>1.70 ± 0.08</td>
<td>1.62 ± 0.08</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.96 ± 12.58</td>
<td>65.23 ± 10.71</td>
<td>0.496</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>80.88 ± 10.46</td>
<td>83.46 ± 11.29</td>
<td>0.268</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.92 ± 5.35</td>
<td>24.69 ± 3.24</td>
<td>0.058</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>118.76 ± 10.94</td>
<td>117.75 ± 14.04</td>
<td>0.822</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.21 ± 7.66</td>
<td>75.39 ± 10.12</td>
<td>0.255</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.49 ± 0.27</td>
<td>5.79 ± 0.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>50.85 ± 18.99</td>
<td>52.15 ± 21.77</td>
<td>0.557</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>115.09 ± 31.70</td>
<td>118.37 ± 24.96</td>
<td>0.462</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>189.58 ± 34.73</td>
<td>193.44 ± 43.45</td>
<td>0.427</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>82.15 ± 55.25</td>
<td>102.33 ± 51.33</td>
<td>0.034</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>91.70 ± 6.36</td>
<td>96.07 ± 10.34</td>
<td>0.133</td>
</tr>
<tr>
<td>LHR</td>
<td>1.51 ± 1.39</td>
<td>1.04 ± 0.75</td>
<td>0.253</td>
</tr>
<tr>
<td>PAR</td>
<td>0.79 ± 0.40</td>
<td>0.54 ± 0.23</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Group 1: healthy young subjects; Group 2: healthy upper middle-aged subjects. Values are expressed as means ± SDs. 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 to amplitude ratio.
3.2.2 Comparison of anthropometric, hemodynamic, and computational parameters between healthy upper middle-aged subjects (Group 2) and type-2 diabetic patients (Group 3)

As shown in Table 2, the age difference between the subjects in Group 2 and Group 3 did not reach significance (55.36 ± 6.15 years vs. 56.82 ± 7.53 years, P = 0.237). Significant differences between the two groups were found in terms of body weight (65.23 ± 10.71 kg vs. 72.95 ± 13.18 kg, P = 0.038), waist circumference (83.46 ± 11.29 cm vs. 94.98 ± 10.68 cm, P = 0.001), and BMI (24.69 ± 3.24 kg/m^2 vs. 27.66 ± 4.47 kg/m^2, P = 0.006). In the blood samples, the two groups also presented significant differences in HbA1c (5.79 ± 0.35 % vs. 8.48 ± 1.99 %, P < 0.001) and fasting blood sugar (96.07 ± 10.34 mg/dL vs. 153.36 ± 57.72 mg/dL, P < 0.001). Furthermore, the two groups differed significantly in the LHR (1.04 ± 0.75 vs. 0.59 ± 0.40, P = 0.001) and the PAR (0.54 ± 0.23 vs. 0.47 ± 0.26, P = 0.009).

Table 2. Comparison of physiological parameters, blood samples, HRV, and PAR between healthy upper middle-aged subjects and type-2 diabetic patients.

<table>
<thead>
<tr>
<th></th>
<th>Group 2 (n = 28)</th>
<th>Group 3 (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.36 ± 6.15</td>
<td>56.82 ± 7.53</td>
<td>0.237</td>
</tr>
<tr>
<td>Body height (m)</td>
<td>1.62 ± 0.08</td>
<td>1.62 ± 0.10</td>
<td>0.857</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>65.23 ± 10.71</td>
<td>72.95 ± 13.18</td>
<td>0.038</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.46 ± 11.29</td>
<td>94.98 ± 10.68</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>24.69 ± 3.24</td>
<td>27.66 ± 4.47</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>117.75 ± 14.04</td>
<td>125.32 ± 13.47</td>
<td>0.085</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75.39 ± 10.12</td>
<td>76.86 ± 11.30</td>
<td>0.605</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.79 ± 0.35</td>
<td>8.48 ± 1.99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>52.15 ± 21.77</td>
<td>42.00 ± 9.75</td>
<td>0.087</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>118.37 ± 24.96</td>
<td>118.67 ± 32.62</td>
<td>0.281</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>193.44 ± 43.45</td>
<td>181.14 ± 37.29</td>
<td>0.117</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>102.33 ± 51.33</td>
<td>129.21 ± 71.56</td>
<td>0.157</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>96.07 ± 10.34</td>
<td>153.36 ± 57.72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LHR</td>
<td>1.04 ± 0.75</td>
<td>0.59 ± 0.40</td>
<td>0.001</td>
</tr>
<tr>
<td>PAR</td>
<td>0.54 ± 0.23</td>
<td>0.47 ± 0.26</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Group 2: healthy upper middle-aged subjects; Group 3: type-2 diabetic patients. Values are expressed as means ± SDs. 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 to amplitude ratio.

3.3 Correlation between risk factors and PAR

Figure 6 shows that among the 61 healthy subjects between the ages of 21 and 67 in Group 1 and Group 2, the PAR and age presented a significantly negative linear relationship (R = -0.240, P = 0.031). As shown in Fig. 7, a negative linear relationship also existed between the PAR and glycosylated hemoglobin among the diabetic patients (Group 3) (R = -0.422, P = 0.013).

Analysis of the correlation between risk factors and the PAR in all of the subjects (Group 1, Group 2, and Group 3) is presented in Table 3. As can be seen, age (R = -0.373, P < 0.001), waist circumference (R = -0.386, P < 0.001), BMI (R = -0.370, P < 0.001), HbA1c (R = -0.444, P < 0.001), triglyceride (R = -0.349, P < 0.001), and fasting blood sugar (R = -0.370, P < 0.001) are all negatively correlated to the PAR.

Table 3. Correlation between risk factors and PAR in all participants.

<table>
<thead>
<tr>
<th></th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>R = -0.373, P &lt; 0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>R = -0.386, P &lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>R = -0.370, P &lt; 0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>R = -0.444, P &lt; 0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>R = -0.349, P &lt; 0.001</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>R = -0.370, P &lt; 0.001</td>
</tr>
</tbody>
</table>

BMI = body mass index; HbA1c = glycosylated hemoglobin.

4. Discussion

The assessment of BRS typically requires invasive methods to measure continuous changes in blood pressure. Catheters are inserted into the aorta to measure blood pressure and changes in the blood pressure are recorded after the injection of drugs. BRS is 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 photoplethysmography 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, this study substituted the amplitude of pressure pulse acquired by our instruments at the wrist for blood pressure to assess...
baroreflex activity. Although counterpressure may affect the amplitude of a pressure pulse, the proposed system showed good reproducibility in three consecutive measurements of the PAR in healthy young subjects (Fig. 4). For convenience, commercialized instruments use PPI as a substitute for RRI in calculating BRS. This study demonstrated good agreements between PPI and RRI (Fig. 2) and in measuring the PAR using either PPI or RRI (Fig. 3). The PAR was compared with another useful parameter of autonomic nerve function, the LHR. Figure 5 shows a strong agreement between these two indices. This demonstrates the feasibility of using the PAR as an index for autonomic function assessment. Therefore, this proposed parameter can be used to assess cardiac autonomic function using an easily assembled instrument. This parameter can be used in clinical or pharmacological studies in the future.

There is a significant difference of the PAR between healthy young subjects (Group 1) and healthy upper middle-aged subjects (Group 2) in Table 1 (0.79 ± 0.40 vs. 0.54 ± 0.23, P = 0.032). Although the LHR decreased with age [31], significant differences in the LHR were not found in this study. This may be a result of the small sampled population. Nevertheless, the PAR showed a significant difference between these two groups. We propose that development of autonomic dysfunction and impairment of baroreflex may occur at different stages of diabetes [32]. In addition, a previous study [33] showed that the BRS decreases with increasing age. In this study, the PAR values for Group 1 were significantly higher than those for Group 2 (0.79 ± 0.40 vs. 0.54 ± 0.23, P = 0.032). This demonstrates that the PAR results are identical to the BRS results.

Diabetes is usually associated with autonomic dysfunction [34]. Table 3 shows significant differences in the LHR and the PAR between healthy upper middle-aged subjects and type-2 diabetic patients (1.04 ± 0.75 vs. 0.59 ± 0.40, P = 0.001; 0.54 ± 0.23 vs. 0.47 ± 0.26, P = 0.009, respectively). The PAR was also inversely associated with risk factors of cardiac autonomic dysfunctions including age and glycosylated hemoglobin (Figs. 6 and 7). Because of small sample size, there was no significant association between PAR and age and glycosylated hemoglobin. However, there are statistically significant relations between the PAR and other risk factors. This is similar to the findings of previous research on the relationships between BRS and diabetes and between BRS and age [3]. As shown in Table 3, negative linear relationships were found between the PAR and BMI (R = -0.370, P = 0.001) and between the PAR and triglyceride (R = -0.349, P < 0.001). Similar results were found in previous studies using commercial instruments to assess BRS [34,35].

Currently available instruments use calibrated blood pressure and PPI acquired from photoplethysmography to assess the baroreflex activity using the spontaneous sequence technique. The BRS is quantified as the relationship between the changes of SBP and PPIs. In this study, the amplitude of a pressure pulse was substituted for the systolic pressure to assess the spontaneous baroreflex activity to simply the method. Although the radial artery pulse signal was not converted to a blood pressure in this study, it is believed that the application of either blood pressure or pulse amplitude does not affect the results of our calculations because the BRS is calculated using the slope of continual variables (that is, continually increasing or continually decreasing RRI and SBP). In the measurement of the PAR, the slopes of continual variables PPI and pulse amplitude are calculated. Our device was not compared with conventional instruments; however, the reproducibility of our measurements was demonstrated using the linear regression and the reliability of PAR with another autonomic nerve index, the LHR, was demonstrated in healthy subjects. Furthermore, the PAR decreased with age and is related to several risk factors, as has been found for the BRS. A pharmacological study with angiotensin agents or a cohort study with large populations will be helpful to confirm the applicability of the PAR.

5. Conclusion

This study used the spontaneous sequence technique to analyze a cardiac autonomic index, the PAR, derived from wrist pressure pulse amplitude and PPI. Compared with available commercial devices, our instrument has lower cost, requires less time, and is more convenient, as there is no need for converting pulse signals and calibration. It can be used for the simple assessment of cardiac autonomic function for clinical applications and homecare.

Acknowledgements

This research was party supported by National Science Council of Taiwan under grants NSC 100-22221-E-259-030-MY2, NSC 101-2221-E-259-012, and NSC 101-2221-E-303-002.

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