Original Article

Relationship between Brachial-Ankle Pulse Wave Velocity and Heart Rate Variability in Young Japanese Men

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Mariko NISHIKITANI*, and Eiji YANO*

This study examined the relationship between arterial stiffness and autonomic nervous function in a young population. A cross-sectional study was conducted on 382 Japanese males, aged 24 to 39 years, who worked at the same information service company. Brachial-ankle pulse wave velocity (baPWV) was measured using an automatic waveform analyzer, and the spectral power of heart rate variability in the low frequency (LF: 0.04–0.15 Hz) and the high frequency (HF: 0.15–0.40 Hz) band was evaluated by the maximum entropy method. LF/HF and HF were used as the indicators of sympathetic and parasympathetic nervous activity, respectively. Psycho-hormonal responses were examined by the Profile of Mood State (tension-anxiety and anger-hostility scales) and Hamilton’s Depression Scale with serum cortisol and catecholamine levels. In a univariate analysis, baPWV was positively associated with the following variables (all \( p < 0.05 \)): LF/HF, age, body mass index, systolic and diastolic blood pressures, heart rate, serum total cholesterol and triglycerides, blood glucose, and plasma cortisol and noradrenaline. Multiple regression analysis indicated that LF/HF was an independent predictor of baPWV (\( p < 0.05 \)), after controlling for significant effects of age, systolic blood pressure, and plasma noradrenaline levels. There was no significant effect of HF on baPWV in this multivariate analysis. Neither mood state nor health-related lifestyle factors such as smoking were significant. It was suggested that baPWV is closely associated with sympathetic nervous activity in young men. (Hypertens Res 2004; 27: 925–931)

Key Words: arterial stiffness, brachial-ankle pulse wave velocity, heart rate variability, mood state, stress

Introduction

Increased arterial stiffness is one of the pathological states of vascular diseases, and is closely associated with atherosclerotic cardiovascular diseases (CVD). Pulse wave velocity (PWV) is known to be an indicator of this arterial stiffness, and the measurement of brachial-ankle PWV (baPWV) has recently been applied as a simple and reliable marker to screen the general population for intensive prevention of CVD (1–6).

It has been reported that major contributing factors to baPWV were age, blood pressure (BP), and gender in a Japanese population (3). A more recent study revealed that baPWV itself was an independent risk factor for the presence of CVD, after adjusting for the significant effects of diabetes and hyperlipidemia in male Japanese patients (6). However, there have been few studies focusing on the specific relationship between baPWV and autonomic nervous function. If hyperactivity of sympathetic nervous function were to be clearly
linked to the increase of baPWV, then preventive interventions, such as relaxation training for lowering BP (7–10) and for general stress management (11, 12), would be effective for those with high CVD risks in the early stages. Moreover, the 7th report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) stated that those with 120–139 mmHg systolic BP (SBP) or 80–89 mmHg diastolic BP (DBP) are to be regarded as “prehypertensive” and should adopt lifestyle modifications while they are young (13, 14). We therefore considered that it would be meaningful to clarify the specific role of autonomic nervous function on baPWV in a young population, and to take the effects of BP and other CVD risk factors into account.

Analysis of heart rate (HR) variability has proven to be a powerful tool in the investigation of autonomic control of the heart and now is the most common method used to provide non-invasive indicators of the autonomic nervous system (15). The purpose of the present study was to examine the relationship between baPWV and HR variability, utilizing the routine health checkups in a cohort of workers.

Methods

Study Setting and Subjects

The investigation was carried out at 8:30–11:30 AM between June and July, 2003 in the course of a periodic health check-up in a Japanese information service company. The company is located in the central area of Tokyo, and offers Information-Technology (IT) consultation, system integration solutions, and data management. Because subjects did not include blue-collar workers who were required to undergo special examinations relating to their jobs, the examinations were performed along with the regular employer-sponsored screening programs mandated by the Japanese Industrial Safety and Health Law (16), which were done under contract by the clinical staff of a medical company.

Among the approximately 1,000 employees, the 526 who were younger than 40 years received annual check-ups in the health center of the company. Those aged 40 years or older were referred to an independent health examination center outside the company. The check-ups were mandatory and therefore the attendance rate was 100%. Female workers were excluded from analysis because of the small sample size (n = 89) and the hormonal effects of the menstrual cycle on HR variance and other variables. Among the 437 male subjects, those with arrhythmia in electrocardiograph (n = 26) and those under treatment for coronary heart disease (n = 5), hypertension (n = 2), diabetes mellitus (n = 2), or hypercholesterolemia (n = 1) were also excluded from the analysis. In addition, 19 subjects with an ankle-brachial pressure index (ABI) of less than 0.9 were excluded because their low ABI range indicated that they would probably have arteriosclerosis obliterans, which would result in a loss of PWV (4, 17). Therefore, the final study group consisted of 382 male workers with a mean age of 30 years.

The study design was approved by the Committee of Labor and Safety in the company, and all participants provided their written informed consent to participate.

baPWV

All the subjects were instructed to refrain from breakfast, coffee, and smoking on the morning of the checkups in order to obtain the most accurate data possible. baPWV, BP, and ankle-brachial pressure index were simultaneously measured using an automatic waveform analyzer (VaSera VS-1000; Fukuda, Tokyo, Japan). Measurements were taken with subjects lying in a supine position after resting for at least 5 min. Occlusion and monitoring cuffs were placed around both sites of the upper and lower extremities of subjects.

The pulse-wave sampling rate of the analyzer was 1 kHz. By identifying both the peak and bottom points in the pulse-wave cycle, the amplitude (peak - bottom) was calculated, and an inflection point (i.e., d²/dt² wave-height = 0) was mathematically determined between the bottom point and peak point (Fig. 1). Between the bottom point and inflection point of the pulse-wave, a front point was defined as the most distant point from a straight line whose x-intercept was set back from the bottom point by constant time and whose slope was based on the value of the pulse-wave amplitude (Fig. 1). This means of determining the wave front point is an original method associated with the VaSera VS-1000 System, and has been submitted for a patent.

The time interval between the wave front of the brachial
waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle ($\Delta T_{ba}$). The path length from the heart to the brachium is referred to as $L_a$, and that from the heart to the ankle is designated $L_b$. $(L_a - L_b)$ was estimated automatically according to the body height of the subject, using the following equation: $L_a - L_b = 0.59 \times \text{body height (cm)} + 14.2$. baPWV was then calculated as follows: $\text{baPWV} = \frac{(L_a - L_b)}{\Delta T_{ba}}$. The mean of the right- and left-sided baPWV at the second measurement was used for analysis in the present study.

HR Variability

A regular screening for heart disease was then performed by electrocardiography, and the R–R interval data over a period of 5 min were stored on a personal computer. To obtain stable data, only the R–R intervals over the last 1 min were used for analysis.

Spectral analysis using the maximum entropy method (18) was applied to the time-series data of HR variability. Although fast Fourier transform and the autoregressive method have been widely used for spectral analysis, these methods have some weaknesses, such as poor resolution due to the effect of the window functions and the small lag time. The maximum entropy method was developed to overcome these disadvantages and was considered to have a high degree of resolution despite the limited duration of data gathering (19). Two frequency bands of interest were considered: a low frequency (LF: 0.04–0.15 Hz) and a high frequency (HF: 0.15–0.40 Hz) band. LF/HF was considered to reflect sympathethic nervous activity, and HF to reflect parasympathetic nervous activity (7, 8, 20).

CVD Risk Factors

Based on the previous baPWV studies (3, 21, 22), the following physiological risk factors of CVD were assessed: age, body mass index (BMI), BP, HR, serum total-choles Terol (T-cho), serum triglyceride (TG), and fasting blood sugar (FBS). In addition to these traditional CVD risk factors, plasma catecholamine (adrenaline, noradrenaline, and dopamine) and cortisol levels were assessed. Because the study was conducted in the setting of a routine health examination, a blood catheter was not used for measurement of plasma catecholamine and cortisol levels. Instead, blood was directly taken through the cubital vein after 15 min of supine rest. T-cho, TG, and FBS were measured by standard laboratory techniques. After centrifugation by 1,500  $\times$ g for 10 min at 4 °C, the supernatant volume was stored at - 40 °C until the assay. Plasma catecholamine was measured by routine high-performance liquid chromatography (23), and plasma cortisol was measured by radioimmunoassays (24).

Health-related lifestyle factors (alcohol consumption, smoking, and lack of exercise) were also examined in this interview. The three variables were dichotomized, with regular drinking once a week or more frequently, current smoking, and irregular exercise of less than once a week defined as positive (16).

Psychological Conditions

Considering the possible effects of mood states on autonomc nervous function, two questionnaires, the Profile of Mood States (POMS) and 21-item Hamilton Depression Scale (HAM-D) were administered to each subject during the examination. The reliability and validity of the Japanese version of the POMS have been examined (25, 26), and the POMS tension-anxiety and anger-hostility scales were analyzed in this study. The HAM-D questionnaire assesses the degree of depression, and has frequently been used in a clinical setting, such as in trials of the pharmacological effects of new antidepressants (27).

Statistical Methods

Data analyses were conducted using the SAS statistical package (SAS Institute Inc., Cary, USA) (28). All the tests were two-sided, and values of $p < 0.05$ were considered to indicate statistical significance.

First, Spearman’s correlational analysis was conducted to assess the association of baPWV with HR variability (LF/HF and HF), cardiac risk factors, and psychological conditions, because the distribution of baPWV was not found to be normal by Shapiro-Wilk test ($p > 0.05$). Then, the values of HR variability were transformed into four ordinal categories (i.e., lowest, lower, higher, and highest) using the cut-off points of three quartiles (25%, median, and 75%), and one-way analysis of variance (Bonferroni method) was used to analyze the differences in baPWV among the four groups. This analysis was specifically intended to confirm the trend of baPWV corresponding to the relative ranks of LF/HF and HF, because it has often been pointed out that the absolute values tend to vary greatly among subjects.

Finally, a multiple regression analysis was used to examine whether baPWV was independently predicted by LF/HF or HF, after controlling for the significant effects of other cardiovascular risk factors. Candidate predictors selected in this multivariate model were the variables significantly correlated to baPWV by a simple correlational analysis.

Results

Means ± SD of baPWV were 11.1 ± 1.3 m/s, and ranged from 8.2 to 16.5. baPWV was significantly and positively associated with LF/HF, age, BMI, SBP and DBP, HR, T-cho, TG, FBS, and plasma cortisol and noradrenaline levels (Table 1). In contrast, it was significantly and negatively associated with HF. Plasma adrenalin and dopamine levels, POMS tension-anxiety and anger-hostility scores, HAM-D scores, and health-related lifestyle factors of alcohol con-
Table 1. Associations of Brachial-Ankle Pulse-Wave Velocity (baPWV) with Heart Rate Variability and Physical, Psychological and Behavioral Variables in 382 Young Men

<table>
<thead>
<tr>
<th>Variables</th>
<th>Means ± SD [range]</th>
<th>Correlation to baPWV&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate variability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of low to high frequency (LF/HF)</td>
<td>2.5 ± 2.5 [0.1–15.8]</td>
<td>0.185 &lt;0.0005</td>
</tr>
<tr>
<td>HF (ms&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>480.5 ± 588.0 [20.5–4,582]</td>
<td>-0.208 &lt;0.0001</td>
</tr>
<tr>
<td>Physiological variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>30.4 ± 5.0 [24–39]</td>
<td>0.380 &lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>22.6 ± 3.0 [16.2–34.3]</td>
<td>0.107 &lt;0.05</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119.3 ± 11.7 [92–160]</td>
<td>0.390 &lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>72.1 ± 9.2 [50–108]</td>
<td>0.367 &lt;0.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.3 ± 10.1 [44–102]</td>
<td>0.266 &lt;0.0001</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>183.5 ± 35.9 [93–311]</td>
<td>0.221 &lt;0.0001</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>109.5 ± 83.5 [28–814]</td>
<td>0.188 &lt;0.0005</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>89.7 ± 11.2 [72–250]</td>
<td>0.136 &lt;0.01</td>
</tr>
<tr>
<td>Plasma cortisol (pg/ml)</td>
<td>14.6 ± 5.1 [0.6–35.4]</td>
<td>0.140 &lt;0.01</td>
</tr>
<tr>
<td>Plasma catecholamine (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline</td>
<td>0.05 ± 0.04 [0.01–0.65]</td>
<td>0.078 NS&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>0.38 ± 0.14 [0.11–1.30]</td>
<td>0.128 &lt;0.05</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.01 ± 0.01 [0.01–0.06]</td>
<td>0.070 NS</td>
</tr>
<tr>
<td>Psychological variables, scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMS tension-anxiety</td>
<td>9.8 ± 6.2 [0–35]</td>
<td>0.013 NS</td>
</tr>
<tr>
<td>POMS anger-hostility</td>
<td>6.0 ± 6.7 [0–36]</td>
<td>0.064 NS</td>
</tr>
<tr>
<td>Hamilton depression scale</td>
<td>6.8 ± 4.8 [0–27]</td>
<td>0.001 NS</td>
</tr>
<tr>
<td>Dichotomized variables (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol (1: ≥1 per week / 0: &lt;1 per week)</td>
<td>288 (75%) / 94 (25%)</td>
<td>0.055 NS</td>
</tr>
<tr>
<td>Smoking (1: current / 0: past or never)</td>
<td>163 (43%) / 219 (57%)</td>
<td>0.001 NS</td>
</tr>
<tr>
<td>Lack of exercise (1: never / 0: ≥1 per week)</td>
<td>258 (68%) / 124 (32%)</td>
<td>0.001 NS</td>
</tr>
</tbody>
</table>

<sup>a</sup> Spearman’s correlation coefficient. <sup>b</sup> NS, not significant (p>0.05).

LF/HF was significantly associated with the following CVD risk factors (Spearman’s correlation coefficient): age (0.149, p<0.005), BMI (0.129, p<0.01), SBP (0.177, p<0.0005), HR (0.199, p<0.0001), T-cho (0.150, p<0.005), TG (0.131, p<0.01), plasma adrenaline (0.132, p<0.01), and plasma noradrenaline (0.111, p<0.05). As for HF, it was significantly associated with age (-0.404, p<0.0001), BMI (-0.189, p<0.0001), SBP (-0.216, p<0.0001), DBP (-0.208, p<0.0001), HR (-0.492, p<0.0001), T-cho (-0.197, p<0.0001), TG (-0.253, p<0.0001), FBS (-0.171, p<0.0001), plasma cortisol (-0.171, p<0.0005), and lack of exercise (-0.168, p<0.0005).

When LF/HF values were divided into four groups, the mean values of baPWV were found to differ significantly among the four groups by ANOVA. baPWV was significantly increased with the increase of LF/HF by trend test (Fig. 2). When HF values were divided into four groups, the mean values of baPWV were found to differ significantly among the four groups by ANOVA. However, the trend was insignificant (p>0.05) among the HF groups by trend test (Fig. 2).

The multiple regression analysis indicated that LF/HF significantly predicted baPWV after controlling for the effects of cardiac risk factors (model 1 in Table 2), but failed to find such significant associations between HF and baPWV (model 2 in Table 2). The effects of age, SBP, and plasma noradrenaline levels were significant in both models (Table 2).

Discussion

In the present study, baPWV was positively associated with LF/HF, and negatively associated with HF by correlational analysis. The trend was statistically confirmed between baPWV and LF/HF, after dividing the values of LF/HF into four ordinal categories. Furthermore, LF/HF significantly predicted baPWV in the multivariate analysis, after adjusting for age, SBP, and plasma noradrenaline levels. As far as we know, this was the first human study to show a clear, quantitative relationship between baPWV and sympathetic nervous tone, after taking the effects of important variables such as...
BP, HR, BMI, T-cho, and FBS into consideration. In support of the present findings, recent studies have linked sympathetic nervous system hyperresponsivity to accelerated development of carotid atherosclerosis in human subjects and monkeys (29–31). However, PWV is considered to assess functioning of both muscular and elastic arteries, and the results of the present studies did not permit any conclusions as to whether hyperactivity of the sympathetic nervous system was associated with the stiffness of elastic arteries or whether it was simply a reflection of the tension of muscular arteries. Further studies will be needed to clarify the exact mechanism mediating LF/HF and baPWV.

Contrary to the clear associations of baPWV with HR variability and physiological variables, no psychological or health-related lifestyle variables were significantly associated with baPWV in the present study. These results were unexpected, since type A behavior patterns or specific mood states like anger and hostility have been known to predict arteriosclerosis (32, 33), and because we have speculated that an accumulation of negative feelings and unhealthy lifestyle factors causes arterial stiffness through hyperactivity of sympathetic nervous function (34, 35).

A possible explanation for our findings was that hyperactivity of the sympathetic nervous function might be mainly affected by physiological conditions rather than by the psycho-behavioral variables examined in the present study. This interpretation might be supported by the results that both LF/HF and HF were significantly associated only with physical CVD risk factors such as BMI, SBP, HR, T-cho, and TG in the present study. The second possible explanation is that the method used to monitor psychological and behavioral conditions in the present study may have been inadequate to detect a significant association between such stressed conditions and autonomic nervous function. The monitoring of more objective stressors, including excessive working hours or workload, might be used to examine this possibility in a future study (36).

Third, the significant associations between baPWV and physiological variables without the contribution of psycho-behavioral variables might be a phenomenon specific to young subjects. Although many previous studies have shown that psychological stress induces the elevation of BP and

![Fig. 2. Effects of the ratio of low to high frequency (LF/HF) and high frequency (HF) of heart rate variability on brachial-ankle pulse-wave velocity (baPWV). LF/HF was divided into four groups according to the 25, 50, and 75 percentiles: a lowest group (n = 99, LF/HF < 0.9), lower group (n = 90, 0.9 ≤ LF/HF < 1.7), higher group (n = 92, 1.7 ≤ LF/HF < 3.1), and highest group (n = 101, LF/HF ≥ 3.1). HF was divided into four groups according to the 25, 50, and 75 percentiles (ms²): a lowest group (n = 96, HF < 34), lower group (n = 94, 34 ≤ HF < 101), higher group (n = 93, 101 ≤ HF < 12), and highest group (n = 99, HF ≥ 12). There were significant main effects of LF/HF groups (F = 11.69, p < 0.0001) and HF groups (F = 14.63, p < 0.0001) on baPWV by one-way analysis of variance. LF/HF was also found to have a significant effect through the trend test (p < 0.05).](image-url)

Table 2. Predictors of Brachial-Ankle Pulse-Wave Velocity (n = 382): Results of Multiple Regression Analysis

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope c</td>
<td>p value</td>
<td>Slope</td>
<td>p value</td>
</tr>
<tr>
<td>Heart rate variability (LF/HF or HF)</td>
<td>0.112</td>
<td>&lt;0.05</td>
<td>-0.022</td>
<td>NS a</td>
</tr>
<tr>
<td>Age (years old)</td>
<td>0.242</td>
<td>&lt;0.0001</td>
<td>0.248</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>-0.086</td>
<td>NS</td>
<td>-0.092</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.378</td>
<td>&lt;0.0001</td>
<td>0.343</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0.060</td>
<td>NS</td>
<td>0.079</td>
<td>NS</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>0.058</td>
<td>NS</td>
<td>0.063</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>0.039</td>
<td>NS</td>
<td>0.048</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cortisol (pg/ml)</td>
<td>0.004</td>
<td>NS</td>
<td>0.011</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma noradrenaline (pg/ml)</td>
<td>0.100</td>
<td>&lt;0.05</td>
<td>0.111</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

a Ratio of low to high frequency (LF/HF) was adopted as an independent variable of heart rate variability in model 1 (r² = 0.314).

b High frequency (HF) was adopted as an independent variable of heart rate variability in model 2 (r² = 0.300). c Slope: standardized regression coefficient. d NS, not significant (p > 0.05).

Concerning systolic and diastolic blood pressures, only systolic blood pressure was adopted as an independent variable of blood pressure, considering colliniarity effects between both blood pressures. Concerning serum total cholesterol and triglyceride levels, only serum total cholesterol level was adopted as an independent variable of serum cholesterol level, considering colliniarity effects between the two cholesterol levels.
other variables related to coronary artery disease (CAD) risk factors in young adults, most of the studies used acute and intermediate stress parameters such as an experimental stress test and preparation for examination (37–39). There is thus an urgent need to determine the duration of chronic stress needed to cause cardiovascular changes in the future. If such changes require a long period of time, regular physical examinations would be sufficient to screen young adults with a high risk of CAD.

Finally, the validity of measurement for baPWV should be mentioned in the present study. In various large populations, baPWV has been reported to be a valid, non-invasive method of monitoring arterial stiffness (1–6; 40). However, most of these studies were conducted using a plethysmographic apparatus (PWV/ABI; Colin Co., Ltd., Tokyo, Japan) rather than using the system employed here; accordingly, the validity of the present system should be studied in the near future.

Through a thorough assessment of baPWV in a screening examination, the monitoring of HR variability might be important for detecting individuals with high CAD risks at the early stage.

References


