Abstract

Objective  Pulse wave velocity (PWV) correlates well with arterial distensibility and stiffness and is a useful non-invasive index to assess arteriosclerosis. The present study was conducted to evaluate the validity of noninvasive brachial-ankle PWV (baPWV) measurements in overweight young adults.

Methods  Three hundred and fifty-three students were voluntarily enrolled (mean age: 20±2, 93 women and 260 men). The subjects were divided into three groups: normal (18.5\leq body mass index (BMI) \leq 25 n=120), overweight (25\leq BMI \leq 30 n=164) and obese (BMI \geq 30, n=69). The baPWV was measured using volume-plethysmographic apparatus.

Results  Hypertension and hyperlipidemia were diagnosed in one-third of the subjects of the obese group and nonalcoholic fatty liver disease (NAFLD) was diagnosed in 64% of the obese group. The baPWV in male subjects was significantly higher in the obese group than in the overweight group and in the males with NAFLD than in those without NAFLD. The stepwise linear regression analysis showed that PWV was significantly associated with mean blood pressure (p<0.001) and \gamma-GTP (p=0.03).

Conclusion  Mean blood pressure was a powerful determination for baPWV in the university students. BaPWV may be useful to predict the initial stage of arteriosclerosis and conceivably NAFLD including nonalcoholic steatohepatitis (NASH) in obese young adults.

Key words:  brachial-ankle pulse wave velocity, arteriosclerosis, nonalcoholic fatty liver disease, obesity

Introduction

In recent years, studies have shown that parameters derived from arterial pressure wave other than systolic and diastolic blood pressure provides important information on cardiovascular status. Arterial stiffness represents one of the major hemodynamic factors determining pulse pressure even at an early stage of disease and its changes have been shown to be an independent predictor of hard endpoints in patients with a high cardiovascular risk. Pulse pressure and heart rate constitute other outcomes that may be useful as additional factors in risk assessment for future therapeutic decision making (1). Pulse wave velocity (PWV) is measured from the initial upstroke of pressure wave and constitutes an established index of arterial stiffness. It is directly related to arterial compliance, arterial distensibility and other factors describing arterial stiffness (2). The PWV is not only a good tool for assessing vascular damage, but also an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension (3). There is also accumulated data concerning with the validity of PWV in patients with various vascular diseases related with diabetes mellitus, renal failure and systemic lupus erythematosus (SLE).

Childhood obesity has been increasing in Japan, and especially middle and morbid obesity has hardly improved. The recent increases might be due to changes towards a westernized diet and dietary habits. Complications such as hypertension, serum lipid disorder and fatty liver are also observed in childhood obesity (4). Obesity is a common expression of several diverse interacting genetic, familial and environmental factors. Several endocrinologic and metabolic abnormalities including relative insulin insensitivity and triglyceride formation and lipid mobilization from hypertrophic adipocytes are associated with obesity (5). Childhood obesity is associated with accelerated coronary atherosclerosis in adolescents and young adult men (6). However, there are few observations on PWV in patients with obesity, especially in youth (7).

It has been well established that noninvasive carotid-femoral PWV which is closely related to aortic PWV obtained by invasive methods is a useful marker for both assessing vascular damage and prognosis (8). Recently, an
instrument measuring brachial-ankle PWV (baPWV) using a volume-rendering method was developed. This uses pressure cuffs wrapped on the brachium and ankle and is simple, non-invasive and also suitable for screening a large population (9–12). Yamashina et al recently reported the validity and reproducibility of baPWV measurements. The baPWV correlates well with aortic PW obtained using a catheter-tip manometer, and are significantly higher in coronary artery disease (CAD) patients than in non-CAD patients with risk factors, and are higher in non-CAD patients with risk factors than in healthy subjects without risk factors. The day-to-day variability of baPWV does not correlate with day-to-day variability of blood pressure. The benefit of baPWV in screening for vascular damage in a large population is suggested because of the safety and technical simplicity and short sampling time (12). Therefore, the present study was conducted to evaluate the validity and clinical significance of noninvasive baPWV measurements in overweight young adults.

For editorial comment, see p 688.

Methods

This is a single center and observational study which was conducted at the Health Administration Center in Wakayama University in the spring of 2002 and 2003. Informed consent was obtained from all subjects. Healthy students and overweight students without taking medication and those whose body mass index (BMI) was 18.5 and more were eligible for participation in the study. Demographic data collected at study entry included age, sex, smoking status, alcohol consumption and amount of exercise. Drinking and smoking were defined as regular intake when respective consumption was more than 35 g of ethanol and 5 cigarettes per day, respectively. Having regular exercise habits was defined as 30 minutes or longer exercise more than twice per week.

Serum samples were collected from the subjects in the morning after an overnight fast to measure total cholesterol (TC), triglyceride (TG), LDL-cholesterol, aspartate transaminase (AST), alanine aminotransferase levels (ALT) and gamma-glutamyl transpeptidase (γ-GTP) by standard methods. BMI was recorded as weight (kilograms)/height (meters) squared. The subjects were divided into three groups: normal (18.5≤BMI<25, n=120), overweight (25≤BMI<30, n=164) and obese (BMI≥30, n=69).

Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, and hyperlipidemia was defined as a serum level of TC >220 mg/dl or a TG >150 mg/dl. After blood tests, students who indicated hepatic abnormality (ALT >40 IU/l and or γ-GTP >50 IU/l) had serum levels tested for antibodies of hepatitis B and C virus and abdominal ultrasound examination for diagnosis of nonalcoholic fatty liver disease (NAFLD). Alcoholic or drug-induced hepatitis was excluded by the questionnaire.

Pulse wave velocity

The baPWV was measured using a volume-plethysmographic apparatus (form PWV/ABI; Colin, Co., Ltd., Komaki, Japan). This instrument records PWV, blood pressure, electrocardiogram, and heart sounds simultaneously. The subjects were examined in the spine position after at least 5 minutes rest, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. The cuffs were connected to a plethymographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure. The pulse volume waveforms were recorded using a semiconductor pressure sensor, and the sample acquisition frequency for PWV was set at 1,200 Hz. Volume waveforms for the brachium and ankle were stored, and the sampling time was 10s with automatic gain analysis and quality adjustment.

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 (ΔTba). The path length from the suprasternal notch to the brachium (Lb) or to the ankle (La) was obtained from superficial measurements and was expressed using the following equation: Lb=0.2195 X height of the patient (in cm) –2.0734, La=0.8129 X height of the patient (in cm) +12.328. The following equation was used to obtain baPWV: baPWV=(La-Lb) /ΔTba.

Statistics

Data are expressed as the mean±SD. Statistical analysis was performed using the SPSS soft ware package (SPSS version 11.0 for Windows, Inc, Chicago, IL). Unpaired t test and one-way analysis of variance (ANOVA) were used for comparisons of age and baPWV. Analysis of proportions among the groups was performed by Pearson Chi Square test. Kruskal-Wallis test was used for comparisons of clinical parameters among the three groups. Linear correlations between parameters were performed by the Spearman correlation analysis. Stepwise linear regression analysis was performed between PWV and other parameters. P<0.05 was considered significant.

Results

Three hundred and fifty-three voluntary students (mean age: 20±2, 93 females and 260 males) were enrolled. Demographic and clinical characteristics of the study groups are shown in Table 1. The percent of males and subjects with no exercise habit was higher in the overweight and obese groups than in the normal group. Mean blood pressure, serum TG, LDL-cholesterol, ALT, γ-GTP and baPWV values were significantly higher and HDL-cholesterol levels
were significantly lower in the overweight and obese groups than in the normal group (Table 2). NAFLD was diagnosed in all subjects with abnormal high value of $\gamma$-GTP. Hyper-tension and hyperlipidemia were diagnosed in one-third subjects of the obese group and NAFLD was diagnosed in 64% of the obese group (Table 3). The baPWV in males was significantly higher than that in females (1,178±157 vs 1,009±118 cm/sec, $p<0.001$, Fig. 1). If the subjects were restricted to males, baPWV was significantly higher in the obese than in the overweight subjects (1,217±137 vs 1,157±137 cm/sec, $p=0.02$, Fig. 2), and was significantly lower in the male subjects with regular exercise habits than those without exercise habits (1,146±184 vs 1,194±144 cm/sec, $p=0.048$). Moreover, baPWV was significantly higher in the males with NAFLD than those without NAFLD (1,200±150 vs 1,158±129 cm/sec, $p=0.04$, Fig. 3). The baPWV in male correlated significantly with age, mean blood pressure, TG, ALT, $\gamma$-GTP ($r=0.28$, 0.65, 0.14, 0.26, 0.32, Table 4). However, the stepwise linear regression analysis showed that the baPWV was significantly associated with only mean blood pressure ($p<0.001$) and $\gamma$-GTP ($p=0.03$) (Table 5).

### Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age Mean (SD)</th>
<th>Gender Male (%)</th>
<th>Smoking (%)</th>
<th>No exercise habit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal n=120</td>
<td>20 (2)</td>
<td>66.6</td>
<td>8.8</td>
<td>33.9</td>
</tr>
<tr>
<td>Overweight n=164</td>
<td>20 (2)</td>
<td>73.8</td>
<td>8.1</td>
<td>40.7</td>
</tr>
<tr>
<td>Obese n=69</td>
<td>20 (2)</td>
<td>85.5</td>
<td>8.8</td>
<td>48.5</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.21*</td>
<td>0.02**</td>
<td>0.97**</td>
<td>0.07**</td>
</tr>
</tbody>
</table>

*One way analysis of variance, **Pearson X$^2$.

Mean blood pressure was a powerful determination for baPWV in university students as previously shown in patients (13–17). In hypertensive populations, pulse pressure and PWV are significantly and independently associated with cardiovascular amplifications (18). In multivariate models of logistic regression analysis, PWV is significantly associated with all-cause and cardiovascular mortality, independent of previous cardiovascular diseases, age, and diabetes in patients with essential hypertension. By contrast, pulse pressure is not significantly and independently associated with mortality (3).

It is known that multiple metabolic disorders are present in most obese patients, and obesity, particularly visceral adiposity, contributes to the clustering of many other risk factors of CAD, such as hypertension, insulin resistance/type 2 diabetes and dyslipidemia. Obesity is a major modifiable CAD risk factor, and the benefits of weight loss are numerous, leading to improvements in several co-morbidities (19). It has been shown that obesity-induced early events in the genesis of atherosclerosis start in childhood. Severe obesity in children is associated with arterial wall stiffness and endothelial dysfunction (20).

In the present study, baPWV was significantly higher in the obese group than in the overweight group, however, the BMI, TG and HDL were not significantly linked to the baPWV as recently reported (9, 21, 22). Li et al reported that in 835 young adults followed-up over an average period of 26.5 years since childhood, independent predictors of baPWV were systolic blood pressure in childhood and systolic blood pressure, HDL-C, TG, and smoking in adulthood (23). On the other hand, it is demonstrated that statins which are antihyperlipidaemic medicine can reduce PWV in hyperlipidaemic hypertensive patients without any effect on blood pressure (24). Blood pressure seems to be the most important predictor of initial stage of arteriosclerosis and the serum lipids within the limited levels or mild obesity might not reflect the early stage of aortic stiffness especially in simple obese

### Table 2. Clinical Parameters in Control, Overweight and Obese Groups

<table>
<thead>
<tr>
<th></th>
<th>TG mg/dl</th>
<th>LDL-C mg/dl</th>
<th>HDL-C IU/l</th>
<th>ALT IU/l</th>
<th>$\gamma$-GTP IU/l</th>
<th>MBP (right)</th>
<th>baPWV (right)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal n=120</td>
<td>61±33</td>
<td>95±24</td>
<td>60±13</td>
<td>17±11</td>
<td>18±8</td>
<td>89±11</td>
<td>1,108±187</td>
</tr>
<tr>
<td>Overweight n=164</td>
<td>92±63</td>
<td>112±27</td>
<td>52±10</td>
<td>27±23</td>
<td>26±19</td>
<td>91±10</td>
<td>1,124±147</td>
</tr>
<tr>
<td>Obese n=69</td>
<td>121±76</td>
<td>115±31</td>
<td>49±11</td>
<td>64±54</td>
<td>43±28</td>
<td>96±11</td>
<td>1,183±155</td>
</tr>
<tr>
<td>$P$ value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.015</td>
</tr>
</tbody>
</table>

children and in university students.

On the other hand, baPWV in male subjects was significantly higher in the males with NAFLD than in the males without NAFLD and was associated with \( \gamma \)-GTP insensibly, but independently. It is shown that a rise in serum \( \gamma \)-GTP levels in nondrinkers depends largely on the progression in fatty change in the liver cells accompanying increases in the size of body mass. There is a close association between the development of fatty liver and hypertension in obese persons (25, 26). Ikai et al reported that serum \( \gamma \)-GTP levels correlate with blood pressure independently of age and BMI and the changes in blood pressure during a five-year period correlate with the changes in \( \gamma \)-GTP levels (26). They suggested that hypertension in obese people relates at least partly to hyperinsulinemia associated with progression in hepatic steatosis (26).

NAFLD is common in obese children and is a growing problem, given the increase in prevalence of obesity. In the present study, the second third subjects of the obese group had elevated serum transaminase levels caused by NAFLD.

### Table 3. The Prevalence of Diseases in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Hypertension</th>
<th>Hyperlipidemia</th>
<th>NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Overweight</td>
<td>17%</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>Obese</td>
<td>32%</td>
<td>34%</td>
<td>64%</td>
</tr>
</tbody>
</table>

\( P \) values by Pearson \( X^2 \). NAFLD: nonalcoholic fatty liver disease.

### Figure 1. The right brachial-ankle pulse wave velocity (baPWV) in males and females. Results are expressed as mean ±SD. The baPWV in males was significantly higher than that in females (\( p < 0.001 \), by unpaired \( t \) test).

### Figure 2. The baPWV (right) in males. Results are expressed as mean±SD. The right brachial-ankle pulse wave velocity (baPWV) in males was significantly higher in the obese than in the overweight subjects (\( p = 0.02 \), by ANOVA).

### Figure 3. The baPWV (right) in males. Results are expressed as mean±SD. The right brachial-ankle pulse wave velocity (baPWV) was significantly higher in the males with nonalcoholic fatty liver disease (NAFLD) than in the males without NAFLD (\( p = 0.04 \), by unpaired \( t \) test).
suggesting that obese students should take blood examinations for screening of NAFLD. Moreover, nonalcoholic steatohepatitis (NASH), in which fatty change and inflammation of the liver occur in the absence of excess alcohol intake, is increasingly recognized in obese children (27, 28). NASH can develop into liver cirrhosis and liver failure. No factors that determine increasing fibrosis and histologically advanced disease have been recognized, thus, liver biopsy is recommended in all patients for diagnosis and prognosis (29). The early diagnosis of NAFLD in university students and improvement in their lifestyle may prevent development of NASH in adults.

In conclusion, blood pressure was a powerful determinant for baPWV in university students. The baPWV was associated with \( \gamma \)-GTP independently and was significantly higher in the males with NAFLD. It is desirable to determine predictive factors of arteriosclerosis and NASH by noninvasive methods, and the present results indicate that baPWV may be useful to predict the initial stage of arteriosclerosis and conceivably NAFLD including NASH in obesity adolescents and young adults. However, there is no data to define whether or not baPWV is a more useful marker to predict CAD compared to the other risk factors, and further prospective studies are necessary to estimate the availability and superiority of baPWV to predict arteriosclerosis and NASH in obese children or young adults.

Table 4. Correlations between baPWV and Blood Factors in Males

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>BMI</th>
<th>TG</th>
<th>TG</th>
<th>HDL</th>
<th>HDL</th>
<th>LDL</th>
<th>LDL</th>
<th>ALT</th>
<th>ALT</th>
<th>( \gamma )-GTP</th>
<th>( \gamma )-GTP</th>
<th>MBP</th>
<th>MBP</th>
<th>baPWV</th>
<th>baPWV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p )</td>
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<tr>
<td>BMI</td>
<td>1</td>
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<tr>
<td>TG</td>
<td>0.40***</td>
<td>1</td>
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<td></td>
<td></td>
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<tr>
<td>HDL</td>
<td>-0.39***</td>
<td>-0.41***</td>
<td>1</td>
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<td></td>
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<tr>
<td>LDL-C</td>
<td>0.19**</td>
<td>0.10</td>
<td>-0.06</td>
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<tr>
<td>ALT</td>
<td>0.40***</td>
<td>0.47***</td>
<td>-0.20**</td>
<td>1</td>
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<td></td>
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<tr>
<td>( \gamma )-GTP</td>
<td>0.32***</td>
<td>0.46***</td>
<td>-0.14</td>
<td>0.23**</td>
<td>0.79**</td>
<td>1</td>
<td></td>
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<tr>
<td>MBP</td>
<td>0.15*</td>
<td>0.16*</td>
<td>-0.07</td>
<td>-0.08</td>
<td>0.25**</td>
<td>0.32***</td>
<td>1</td>
<td></td>
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<tr>
<td>baPWV</td>
<td>0.07</td>
<td>0.14*</td>
<td>-0.05</td>
<td>-0.02</td>
<td>0.26***</td>
<td>0.32***</td>
<td>0.65***</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

Values are Spearman correlation coefficients. BMI: body mass index, MBP: mean blood pressure, baPWV: brachial-ankle pulse wave velocity, HDL-C: HDL-cholesterol, TG: triglycerides, LDL-C: LDL-cholesterol, ALT: alanine aminotransferase, \( \gamma \)-GTP: gamma-glutamyl transpeptidase.

Table 5. Stepwise Linear Regression of baPWV

<table>
<thead>
<tr>
<th>Reg Coeff</th>
<th>SE</th>
<th>Part Adj R2</th>
<th>Sum Adj R2</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP</td>
<td>0.65</td>
<td>105</td>
<td>42.1%</td>
<td>41.8%</td>
</tr>
<tr>
<td>( \gamma )-GTP</td>
<td>0.66</td>
<td>104</td>
<td>1.5%</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

baPWV: brachial-ankle pulse wave velocity, MBP: mean blood pressure, \( \gamma \)-GTP: gamma-glutamyl transpeptidase.

References