Original Article

Brachial-Ankle Pulse Wave Velocity and Metabolic Syndrome in a Japanese Population: The Minoh Study

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To investigate the association between brachial-ankle pulse wave velocity (baPWV) and metabolic syndrome (MS), we examined 374 men and 622 women aged 40 to 69 years who did not have a past history of either coronary heart disease or stroke. We used a modified National Cholesterol Education Program definition of MS that utilizes body mass index instead of waist circumference. Age-adjusted mean values of baPWV were greater when obesity, high systolic and diastolic blood pressures, high triglyceride level, low high-density lipoprotein cholesterol, high fasting glucose level or MS itself were present. baPWV was also associated with fasting insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR) values. Mean values of baPWV (adjusted for age, smoking status, and drinking status) in men with 0, 1, 2, and ≥3 features of MS were 1,409, 1,517, 1,640, and 1,665 cm/s, respectively (p for trend <0.001). The respective adjusted mean baPWV values for women were 1,368, 1,531, 1,547, and 1,661 cm/s (p for trend <0.001). As for insulin resistance, the adjusted mean baPWV values across quartiles of HOMA-IR (lowest to highest) were 1,488, 1,514, 1,566, and 1,624 cm/s (p for trend <0.001) for men. The respective adjusted mean baPWV values for women were 1,395, 1,441, 1,464, and 1,539 cm/s (p for trend <0.001). Our findings indicate that clustered features of MS and insulin resistance are strongly associated with the risk for increased baPWV in Japanese men and women. (*Hypertens Res* 2005; 28: 125–131)

***Key Words*: pulse wave velocity, arterial stiffness, metabolic syndrome, insulin resistance, Japanese**

Introduction

Pulse wave velocity (PWV) obtained by non-invasive automatic devices is an indicator of arterial stiffness and a marker reflecting vascular damages (*1*, *2*). Recent studies have demonstrated that PWV is an independent predictor of cardiovascular mortality in patients with hypertension and diabetes as well as in end-stage renal failure (*3*–*5*).

Although many studies have focused on the fact that increased PWV is involved in various cardiovascular risk factors, such as age, hypertension, diabetes, dyslipidemia, and smoking (*6*–*13*), the studies relating PWV to cardiovascular risk factors found minimal or inconsistent correlations, except for age and hypertension. Because most individuals have one or more cardiovascular risk factors or a cluster of features of metabolic syndrome (MS) *(i.e.*, obesity, glucose metabolism disturbances, abnormal lipids, and high blood pressure), a clinical condition that seems to be mediated by insulin resistance (*14*, *15*), it may not be appropriate to look only at isolated components. MS is most important because of its association with subsequent development of type 2 diabetes

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Table 1. Clinical and Biochemical Characteristics

	Men (n=374)	Women (n=622)
Age (years)	58.1±7.7	57.9±7.2
Body mass index (kg/m^2)	23.9±2.6	22.3±2.9
Systolic BP (mmHg)	121.3±17.5	115.2±18.6
Diastolic BP (mmHg)	76.0±10.1	71.1±10.3
Medication for hypertension (%)	18.7	13.5
Triglycerides (mmol/l)	1.51±1.11	1.11±0.67
HDL cholesterol (mmol/l)	1.50±0.37	1.87±0.46
Fasting glucose (mmol/l)	6.07±1.20	5.48±0.76
Medication for diabetes (%)	4.0	1.0
Brachial-ankle PWV (cm/s)	1,549±288	1,459±284
Body mass index ≥ 25 kg/m^2 (%)	32.6	16.2
BP ≥130/85 mmHg or medication for hypertension (%)	42.0	29.1
HDL cholesterol <1.03 (men) or <1.29 (women) mmol/l (%)	7.8	9.2
Triglycerides ≥1.69 mmol/l (%)	30.5	12.7
Fasting glucose ≥6.1 mmol/l or medication for diabetes (%)	33.7	9.8
Metabolic syndrome (%)	19.8	5.9
Current smoking (%)	32.9	7.9
Current drinking (%)	77.3	37.0
Fasting insulin (μU/ml)	7.2 (8.1–10.9)	6.7 (4.6–9.7)
HOMA-IR	1.96 (1.27–2.95)	1.61 (1.09–2.37)

BP, blood pressure; HDL, high-density lipoprotein; PWV, pulse wave velocity; HOMA-IR, homeostatis model assessment of insulin resistance. Data are means±SD, percentages, or for fasting insulin and HOMA-IR, medians (interquartile ranges).

and coronary heart disease (CHD) (*16*), and the National Cholesterol Education Program (NECP) has proposed a definition for MS to aid in identification of individuals at risk for both CHD and type 2 diabetes (*17*).

Recently, brachial-ankle PWV (baPWV) has begun to be used as a means of measuring PWV (*9–13*). baPWV reflects the stiffness of both central and peripheral arteries (*9–11*), and data obtained using a bilateral baPWV measurement device have been shown to have good reproducibility (*18*). In this report on a cross-sectional study, we used a modified NCEP definition that utilizes body mass index (BMI) in place of waist circumference (*17*) and examined whether baPWV is associated with features of MS and other cardiovascular risk factors among Japanese.

Methods

Subjects

The Minoh Study is designed to clarify risk factors for major diseases, including hypertension, dyslipidemia, and diabetes among Japanese. Three thousand, one hundred and forty two Japanese subjects aged 40 to 69 years who lived in Minoh City, Osaka Prefecture, underwent thorough health checkups conducted by the Minoh Medical Health Center in 2003. Of these 3,142 individuals, 2,108 (67.1%) gave their written, informed consent before participating in this study and for the use of personal information for analysis. The Ethics Committee of Osaka University approved the study. Although all participants were encouraged to undergo baPWV measurement, only 1,011 (48.0%) (385 men and 626 women) did so. Fifteen subjects (1.5%) who had a past history of either CHD or stroke were excluded. The final study population for analysis therefore consisted of 374 men and 622 women.

Data Collection

The participants were asked to fast for at least 10 h and to avoid heavy physical activity for more than 2 h before the examinations. An interviewer assessed the usual weekly intake of alcohol in units of "go" (a traditional Japanese unit of measurement, by volume, corresponding to 23 g of ethanol), which were converted to g of ethanol per day. One go is 180 ml of sake, and corresponds to one bottle (663 ml) of beer, two single shots (75 ml) of whiskey, or two glasses (180 ml) of wine. Subjects who reported consuming ≥0.3 go per week were regarded as current drinkers (*19*). The questionnaire also asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked per day. Subjects who reported smoking at least 1 cigarette per day during the year before the examination were classified as current smokers. BMI, calculated as weight divided by the square of height in m, was used as an index of relative weight. Blood pressure was measured on the right arm by using an automated sphygmomanometer (UDEX-Ⅲ; Ueda, Tokyo, Japan) after a 5-min rest in a quiet room, and the average of the two blood pressure readings was used in the analyses. Blood samples were drawn from an antecubital vein. Serum triglyceride level, high-density lipoprotein (HDL) cholesterol level, glucose level, and insulin level were determined by an Hitachi 7170 autoanalyzer in the laboratory of the Minoh Medical Health Center. Triglycerides and HDL cholesterol were measured enzymatically. Glucose was measured by a hexokinase-glucose dehydrogenase method, and insulin levels were determined with a radioimmunoassay kit. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting insulin (μU/ml)×fasting glucose (mmol/l)/22.5 (*20*).

Table 2. Age-Adjusted Brachial-Ankle Pulse Wave Velocity (PWV) in Relation to Features of the Metabolic Syndrome and Other Cardiovascular Risk Factors

	Risk factor level	Men (n=374)	Women (n=622)	p for within-risk-factor comparison	p for sex comparison
Age (years)	<60	1,431±17	1,335±11	<0.001	<0.001
	≥60	1,649±21	1,600±17		
Body mass index (kg/m^2)	<25	1,531±16	1,454±11	0.031	<0.001
	≥25	1,574±22	1,494±25		
Systolic blood pressure (mmHg)	<130	1,457±14	1,382±10	<0.001	<0.001
	≥130*	1,699±18	1,655±17		
Diastolic blood pressure	<85	1,485±15	1,415±10	<0.001	<0.001
	≥85*	1,673±21	1,641±21		
Triglycerides (mmol/l)	<1.69	1,519±15	1,448±11	<0.001	<0.001
	≥1.69	1,607±23	1,548±28		
HDL cholesterol (mmol/l)	≥1.03 (men) or ≥1.29 (women)	1,539±14	1,454±11	0.036	<0.001
	<1.03 (men) or <1.29 (women)	1,581±34	1,507±28		
Fasting glucose (mmol/l)	<6.1	1,502±15	1,446±10	<0.001	0.002
	≥6.1*	1,632±22	1,594±31		
Metabolic syndrome	No	1,518±14	1,448±10	<0.001	<0.001
	Yes	1,657±28	1,660±40		
Current smoking	No	1,543±15	1,462±10	0.993	<0.001
	Yes	1,550±22	1,449±35		
Current drinking	No	1,504±27	1,476±12	0.539	<0.001
	Yes	1,558±15	1,436±16		
Fasting insulin (μU/ml)	<75th centile	1,522±15	1,440±11	<0.001	<0.001
	≥75th centile	1,604±24	1,529±20		
HOMA-IR	<75th centile	1,515±15	1,437±11	<0.001	<0.001
	≥75th centile	1,609±22	1,555±22		

HDL, high-density lipoprotein; HOMA-IR, homeostatis model assessment of insulin resistance. Values of brachial-ankle PWV are mean±SEM, cm/s. *Subjects with blood pressure medications or hypoglycemic diabetes control are included.

The five thresholds used were BMI ≥25, proposed by the Japan Society for the Study of Obesity (*21*), systolic blood pressure (SBP)≥130 mmHg and/or diastolic blood pressure (DBP)≥85 mmHg, triglyceride level ≥1.69 mmol/l, HDL cholesterol level <1.03 (men) and <1.29 (women) mmol/l, and fasting glucose level ≥6.1 mmol/l (*17*). Individuals met the criteria for high blood pressure or high fasting glucose level if they were currently using blood pressure medications or hypoglycemic diabetes control. Individuals were classified as having MS if they fulfilled three or more of the criteria.

Bilateral baPWV was measured using a Form PWV/ABI device (Nihon Colin, Komaki, Japan). Details about this instrument and its use have been described elsewhere (*11*, *18*). Briefly, the subjects were examined in the supine position. Waveform data was obtained from a volume plethysmographic sensor in cuffs on the right brachium and both ankles, and time intervals (T) between the wave front of the right brachium and that of both ankles were calculated. The distance (L) between the heart and sampling points was calculated automatically according to the subject's height. baPWV was calculated from the following formula: baPWV=L/T ($L=L_a - L_b$, where L_a is the path length from the heart to ankle, and L_b is the path length from the heart to brachium). Since there was a significant positive correlation between left and right baPWV (r=0.967, p<0.001), we used a mean right/left baPWV value during the analysis.

Statistical Analyses

Data on characteristics of the participants are reported as the mean±SD and percentages except when the distribution was strongly skewed, in which case the median and interquartile range are given. Age-adjusted mean values of baPWV in relation to features of MS and other cardiovascular risk factors were calculated by a generalized linear model analysis. Multiple linear regression analysis was also used to test for differences in age-adjusted mean baPWV values between men and women at each level of the respective risk factors and then to test for interactions between levels of the risk factors and sex on mean baPWV values. Male and female subjects were classified as having 0, 1, 2, or ≥3 components of MS. Categories of fasting insulin and HOMA-IR were defined by the follow-

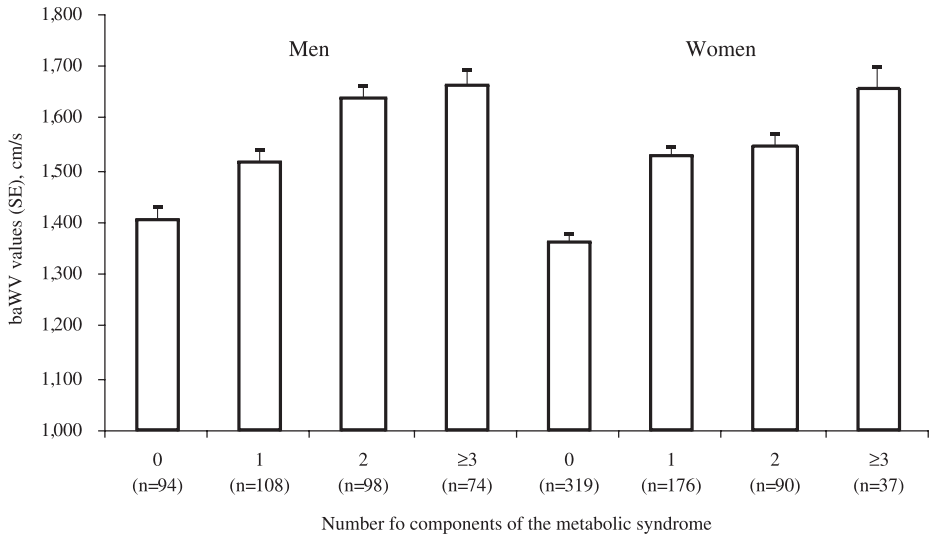

Fig. 1. *Adjusted mean values of brachial-ankle pulse wave velocity (baPWV) and SEM (error bars), according to the number of components of metabolic syndrome. baPWV was adjusted for age, smoking status, and drinking status.*

ing quartiles according to sex: fasting insulin, <5.1, 5.1–7.1, 7.2–10.8, and ≥10.9 μU/ml for men and <4.7, 4.7–6.6, 6.7–9.6, and ≥9.7 μU/ml for women; and HOMA-IR, <1.28, 1.28–1.96, 1.97–2.95, and ≥2.96 for men and <1.09, 1.09–1.61, 1.62–2.36, and ≥2.37 for women. Mean baPWV values were estimated for each group, after adjustment for age, smoking status, and drinking status.

Data were analyzed by using the SPSS/PC statistical package (SPSS, Chicago, USA). All reported p values are two-tailed, and those less than 0.05 were considered to be statistically significant.

Results

The characteristics of the participants in relation to sex are shown in Table 1. Mean age did not differ between men and women ($p=0.559$). The percentage of MS was higher in men than in women ($p<0.001$), and a higher proportion of men than women exceeded thresholds for BMI, blood pressure, triglycerides, and fasting glucose ($p<0.001$ for all). Although HDL cholesterol levels were higher in women than in men ($p<0.001$), a similar proportion of men and women exceeded gender-specific thresholds ($p=0.443$). Mean baPWV and the percentages of current smokers and current drinkers were higher in men than in women ($p<0.001$ for all). The median values of fasting insulin and HOMA-IR were higher in men than in women, and the differences in log-transformed values of these variables were significant ($p<0.001$ for both).

Table 2 shows age-adjusted mean values of baPWV in relation to the features of MS and other cardiovascular risk factors. baPWV values were greater in the subjects with obesity, high SBP, high DBP, high triglyceride level, low HDL cholesterol level, high fasting glucose level or MS itself than in those without. These models explained 0.3%, 28.0%, 10.4%, 2.3%, 0.3%, and 0.4% of the variance in baPWV for obesity, high SBP, high DBP, high triglyceride level, low HDL cholesterol level, and high fasting glucose level, respectively. Only 4.1% of the variance in baPWV was explained by MS itself. baPWV was also associated with age, fasting insulin levels, and HOMA-IR values, but was not associated with current smoking or current drinking. As for the comparison by sex, baPWV values were higher in men than in women across the respective risk factors. There were no significant gender interactions for the features of MS or other cardiovascular risk factors.

Figure 1 shows the mean values of baPWV (adjusted for age, smoking status, and drinking status) according to the number of MS components. Adjusted mean values of baPWV in men with 0, 1, 2, and ≥3 features of MS were 1,409, 1,517, 1,640, and 1,665 cm/s, respectively (p for trend <0.001). The respective adjusted mean baPWV values for women were 1,368, 1,531, 1,547, and 1,661cm/s (p for trend <0.001). A significant gender interaction was not observed ($p=0.579$).

Figure 2 shows the mean values of baPWV (adjusted for age, smoking status, and drinking status) according to HOMA-IR. Adjusted mean values of baPWV in men with <1.28, 1.28–1.96, 1.97–2.95, and ≥2.96 of HOMA-IR were 1,488, 1,514, 1,566, and 1,624 cm/s, respectively (p for trend <0.001). Adjusted mean values of baPWV in women with <1.09, 1.09–1.61, 1.62–2.36, and ≥2.37 of HOMA-IR were 1,395, 1,441, 1,464, and 1,539 cm/s, respectively (p for trend <0.001). There was no significant gender interaction ($p=0.166$). As for the association between baPWV and fasting insulin, adjusted mean values of baPWV in men with <5.1, 5.1–7.1, 7.2–10.8, and ≥10.9 μU/ml of fasting insulin and in women with <4.7, 4.7–6.6, 6.7–9.6, and ≥9.7 μU/ml

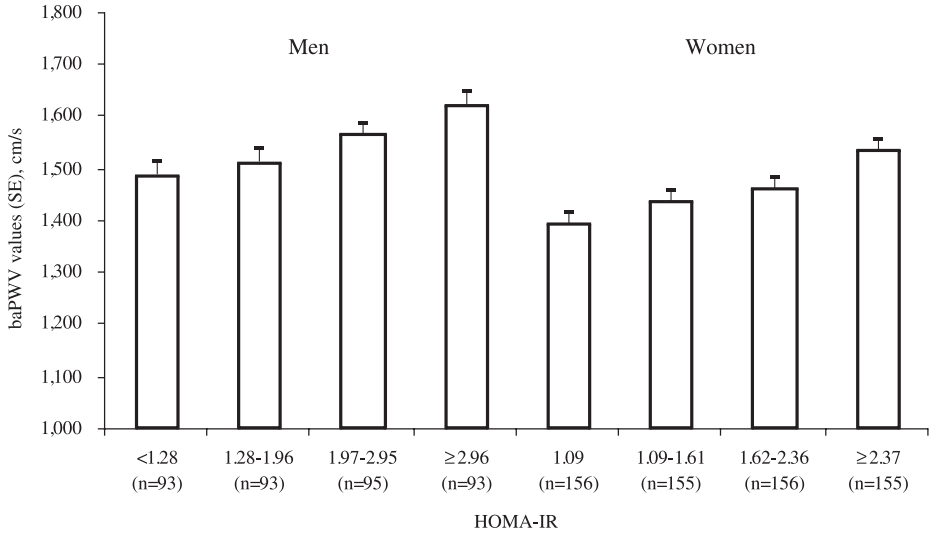

Fig. 2. *Adjusted mean values of brachial-ankle pulse wave velocity (baPWV) and SEM (error bars), according to HOMA-IR. HOMA-IR, homeostasis model assessment of insulin resistance. baPWV was adjusted for age, smoking status, and drinking status.*

of fasting insulin were 1,492, 1,533, 1,561, and 1,604 cm/s, respectively (p for trend <0.001) and 1,402, 1,461, 1,441, and 1,532 cm/s, respectively (p for trend <0.001) (gender interaction: $p=0.572$).

Discussion

In this study, baPWV was greater when obesity, high blood pressure, high triglyceride level, high fasting glucose level or MS itself were present, and high SBP was the strongest determinant for baPWV among the components of MS. baPWV was also associated with fasting insulin levels and HOMA-IR values. From the analyses in relation to the number of components of MS and measures of insulin resistance, baPWV increased in a dose-responsive manner as the number of MS components and values of fasting insulin and HOMA-IR increased in both men and women. These results indicate that the contribution of clustered features of MS appears to be additive, with the subjects with more risk factors having substantially higher baPWV values than those with fewer risk factors in both sexes, and that baPWV is closely associated with insulin resistance (and therefore also with hyperinsulinemia).

It has been reported that carotid intima-media thickness (IMT) and stiffness are associated with several variables of MS, as well as with clustering of the variables of MS (*22*, *23*), and that carotid IMT develops in subjects with insulin resistance (*24*, *25*). Several studies have also shown that aortic stiffness as assessed by aortic PWV is associated with clustered features of MS and insulin resistance (*26*, *27*). However, in these prior studies, there was no clear evidence that MS or insulin resistance were involved in the development of arterial stiffness as assessed by baPWV. In this study, we demonstrated that clustered features of MS and insulin resistance were closely associated with the risk for increased baPWV or increased arterial stiffness. However, the mechanism by which MS or insulin resistance might promote arterial stiffness remains unclear. One explanation for our findings is that the enhancement of arterial stiffness was due to a direct action of insulin on the arterial wall. Insulin promotes the synthesis of collagen, the stiffer form of arterial wall protein, and stimulates hyperplasia and hypertrophy of vascular smooth muscle cells (*28*). Hyperinsulinemia may also indirectly increase arterial stiffness by stimulating the sympathetic nervous system, which could increase arterial smooth muscle tone or blood pressure (*29*).

Our study had some potential limitations. First, baPWV measurements were not available for all participants. The subjects who underwent baPWV measurement were significantly older than those who did not (58.0 years [SD 7.4] *vs.* 55.9 years [SD 8.3]). There was some selection bias with regard to participants who planned to undergo baPWV measurement with the assessment of metabolic markers. The choice to undergo baPWV measurement, however, was not the choice of—and was not specifically recommended by—the physicians. Second, baPWV is an indirect marker of increased arterial stiffness or decreased arterial compliance, and we could not determine the relative influence of arterial wall remodeling on the relationship between cardiovascular risk factors and arterial stiffness. To determine the precise effect of cardiovascular risk factors on arterial stiffness, the use of ultrasound technology, which can estimate both function (stiffness) and morphology, may be preferable. Third, we assessed obesity by using BMI instead of waist circumfer-

ence. The central pattern of distribution, with its higher weighting of waist circumference, is associated with more insulin resistance than is the peripheral pattern of distribution (*30*, *31*). Nevertheless, most physicians routinely assess BMI, whereas the value of waist measurements in clinical practice has not been thoroughly examined. A number of investigations have also shown that BMI is as effective as waist circumference for predicting the development of type 2 diabetes and other metabolic disturbances (*32*, *33*). Moreover, the Japan Society for the Study of Obesity has recently reported that BMI can estimate visceral fat measured by computed tomography as robustly as waist circumference, that obesity-related complications increase in individuals with a BMI ≥25, and that the best combination of sensitivity and specificity for detecting patients with multiple risk factors is a BMI of 25 (*21*). This society suggests that obesity is adequately specified as a BMI ≥25 in Japan, where the prevalence and degree of obesity remain relatively low. Finally, the cross-sectional study design lacks information on the time sequence of events. Further studies will be needed to clarify whether MS or insulin resistance plays an important role in the development of increased baPWV.

Despite these potential limitations, our findings suggest that clustered features of MS and insulin resistance are strongly associated with a risk for increased baPWV in both men and women. Since a decrease in arterial distensibility has been shown to be associated with a risk for cardiovascular mortality (*3*–*5*), baPWV should be taken into consideration as a surrogate end-point in epidemiological studies and as a tool for evaluating cardiovascular risk in clinical practice.

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