REGULAR ARTICLE

Brachial-ankle pulse wave velocity is an independent predictor of incident hypertension in Japanese normotensive male subjects

Hiroki Satoh · Yasuaki Saijo · Reiko Kishi · Hiroyuki Tsutsui

Abstract

Objectives Cardiovascular morbidity and mortality are closely associated with hypertension, however, predictors of incident hypertension have not been fully established. We have conducted a study aimed at evaluating whether brachial-ankle pulse wave velocity (baPWV) is a predictor of incident hypertension.

Methods The relation between baPWV, a noninvasive index of aortic stiffness, and incident hypertension was evaluated in a cohort of 2,278 Japanese normotensive male subjects with a follow-up of 3 years.

Results Of the 2,278 study participants, 151 (6.6%) had incident hypertension during the follow-up. After adjustment for variables, including age, gender, body mass index (BMI), smoking habit, alcohol consumption, diabetes mellitus, hyperlipidemia, family history of hypertension, heart rate, systolic blood pressure, low-density lipoprotein cholesterol, triglyceride, and fasting plasma glucose, multiple logistic regression analysis revealed that baPWV was a significant and independent predictor of incident hypertension with an adjusted odds ratio 1.45 (95% confidence interval 1.17–1.79, $P < 0.01$). In addition, baPWV values >1,380 cm/s indicated a high risk for incident hypertension.

Conclusions Among the Japanese normotensive male subjects participating in this study, BaPWV was a significant and independent predictor of incident hypertension. This result suggests that BaPWV could be a useful screening method to identify normotensive individuals who should be targeted for interventions aimed at preventing the incident hypertension.

Keywords Arterial stiffness · Hypertension · Pulse wave velocity · Cohort studies · Japanese male subjects

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Introduction

The incidence and prevalence of hypertension increase with age. It has been well established that hypertension is associated with increased cardiovascular morbidity and mortality [1–5]. As such, it is of clinical importance to identify normotensive subjects who are at increased risk for developing hypertension and establish the conventional index that can be widely used in routine clinical practice. Previous studies have identified indices of central arterial stiffness assessed by ultrasound that could be used predict future hypertension in normotensive community population [6, 7]. Najjar et al. demonstrated that carotid–femoral pulse wave velocity (PWV), a non-invasive marker of central arterial stiffness [8, 9], could be an independent predictor of the longitudinal increase in blood pressure and incident hypertension in normotensive subjects [10].

Brachial-ankle (ba) PWV has been developed as a marker of arterial stiffness that can be measured using a noninvasive automatic device with relative technical simplicity. baPWV has been shown to be associated with

intima-media thickness of the carotid artery and aortic PWV, a marker of central arterial stiffness [11, 12]. More importantly, baPWV is a significant and independent predictor of cardiovascular morbidity and mortality in patients on hemodialysis and with acute coronary syndrome [13, 14]. However, the relationship between baPWV and the development of hypertension has not been fully established, especially in Japanese normotensive male subjects.

The aim of the study reported here was to determine whether baPWV is an independent predictor of incident hypertension in Japanese normotensive subjects during a 3-year follow-up.

Methods

Study subjects

The study cohort comprised 2,656 Japanese male employees (age range 35–55 years) of a single local government agency who had an annual health checkup between April 2003 and March 2004. Of these, 257 were excluded for the following reasons: past history of coronary artery disease or stroke ($n = 99$), under treatment for hypertension ($n = 114$), low ankle/brachial index <0.9 ($n = 10$), triglyceride values >400 mg/dL ($n = 34$). Ultimately, 121 (4.6%) subjects were lost from observation during the follow-up period. Thus, a total of 2,278 subjects were successfully re-examined at the end of the 3-year follow-up.

This study was approved by the Institutional Ethical Board for epidemiological studies of Hokkaido University School of Medicine. Written informed consent was provided by all subjects.

Baseline data measurements

All subjects were asked to complete a self-administered questionnaire that includes questions on medical history, family history, smoking habit, alcohol consumption, and the frequency of exercise. The questionnaire was distributed to the subjects in advance of their annual check-up and was collected at the examination. Smoking habit and alcohol intake were determined from information collecting during interviews. Subjects who had never smoked and ex-smokers were classified as "nonsmokers". Drinkers were defined as those who consumed alcohol once per week or more. "Non-exercise" referred to the category of individuals who regularly exercised less than once per week. Body mass index (BMI) was calculated as body weight (kg) divided by squared height (m). A blood sample was obtained from the antecubital vein in the morning after an overnight fast and serum was separated. After precipitation by heparin-manganese, total cholesterol and high-density lipoprotein

(HDL)-cholesterol were measured by the phosphotungstate method. Triglyceride was measured enzymatically. Glucose was enzymatically determined by the hexokinase method. Low-density lipoprotein (LDL)-cholesterol values were calculated using Friedwald formula [15]. BaPWV, ankle/brachial index, and heart rate were measured with a volume-plethysmographic apparatus (model BP-203RPE II; Nihon Colin, Tokyo, Japan) [11, 16]. The BaPWV was calculated by time-phase analysis between the right brachial and volume waveforms at both ankles. The ankle/brachial index is the ratio of ankle systolic blood pressure to brachial systolic blood pressure; right and left ankle/brachial indexes were measured simultaneously.

Blood pressure was measured by a trained nurse using a standard mercury sphygmomanometer, with the study subjects in the sitting position after at least a 5-min rest. Blood pressure measurements and information on pharmacological treatments of hypertension were assessed twice during the study in the same manner: at the beginning and the end of the 3-year follow-up.

Incident hypertension

Incident hypertension subjects were those normotensive male subjects who at the beginning of the follow-up had a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at the end of the 3-year follow-up were newly receiving anti-hypertensive drugs.

Statistical analysis

The clinical and biochemical data are expressed as the mean ± standard deviation (SD), as the median value and interquartile range (IQR) for variables with a skewed distribution, and as the number and percentage. The differences in variables between two groups were examined by the Student unpaired t test for approximately normal distributed variables, by the Wilcoxon rank-sum test for triglycerides, and by the χ^2 test for the proportion of gender, alcohol consumption, smoking status, exercise habit, medical history of diabetes mellitus and hyperlipidemia, and family history of hypertension. The data were compared among the groups using analysis of variance (ANOVA), the Kruskal–Wallis test, or the Cochran–Armitage test. The relationship between baPWV values and incident hypertension was investigated using multiple logistic regression analysis adjusted for baseline variables, such as age, alcohol consumption, smoking status, exercise habit, medical history of diabetes mellitus and hyperlipidemia, family history of hypertension, heart rate, BMI, LDL-cholesterol, triglyceride, HDL-cholesterol, fasting plasma glucose, and systolic blood pressure. The baPWV values were divided into quartiles with the following cut-off points: 1,204, 1,288, and

1,380 cm/s for the second, third, and fourth quartiles, respectively. Multiple logistic regression analysis was examined by quartile levels of baPWV values adjusted for baseline variables, such as age, alcohol consumption, smoking status, exercise habit, medical history of diabetes mellitus and hyperlipidemia, family history of hypertension, heart rate, BMI, LDL-cholesterol, triglyceride, HDL-cholesterol, fasting plasma glucose, and systolic blood pressure.

A P value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using the SPSS ver. 11.0 software (SPSS, Chicago, IL).

Results

Of the 2,399 normotensive male subjects at baseline, 2,278 (95.0%) were available for the 3-year follow-up assessment. There were 151 subjects who developed hypertension during the follow-up, with a cumulative incidence of 6.6%. The baseline characteristics of the study subjects according to incident hypertension are presented in Table 1. Compared with normotensive subjects, subjects who developed hypertension during the follow-up significantly had more alcohol consumption, lower exercise habit, diabetes mellitus, hyperlipidemia, and higher values of baseline age, BMI, triglyceride, glucose, and baPWV. They also had significantly higher baseline systolic blood

pressure and diastolic blood pressure, although these values were low the definite values of hypertension.

Odds ratios and the 95% confidence intervals (CI) of the relationship between baPWV and incident hypertension by multiple logistic regression analysis are presented in Table 2. In the age-adjusted model (Model 1), the OR of baPWV (± 1 SD) (142 cm/s) increased by incident hypertension was 2.16 (95% CI 1.80–2.60, $P < 0.001$). In the fully adjusted model (Model 3), this was 1.45 (95% CI 1.17–1.79, $P < 0.01$).

Further assessment of the baseline characteristics of the study subjects stratified by the quartiles of baPWV resulted in values of $\leq 1,204$, 1,205–1,288, 1,289–1,380, and $\geq 1,381$ cm/s for quartiles 1–4, respectively (Table 3). Compared to baPWV values in the lowest quartile, There was a trend for the prevalence of diabetes mellitus, hyperlipidemia, and family history of hypertension, age, BMI, heart rate, systolic and diastolic blood pressure values, and triglyceride and glucose levels to increase from the lowest quartile of baPWV to the highest quartile. The reverse trend was seen for prevalence of exercise.

Table 4 shows the results of the multiple logistic regression analysis evaluating the association between baPWV and incident hypertension as compared with that in the lowest quartile. The highest quartile level of baPWV (>1,380 cm/s) could significantly and independently predict incident hypertension. The age-adjusted OR was 11.05

Table 1 Baseline characteristics of the study subjects in relation to the development of hypertension

Baseline characteristics	Total ($n = 2{,}278$)	Incident hypertension		P value
		No ($n = 2{,}127$)	Yes ($n = 151$)	
Age, years (n)	46 ± 6	46 ± 6	48 ± 5	<0.01
Body mass index (kg/m^2)	23.7 ± 2.8	23.1 ± 2.9	25.4 ± 3.3	<0.001
Smoking (n, %)	1,164 (51.1%)	1,097 (51.6%)	67 (44.4%)	0.09
Alcohol (n, %)	1,640 (72.0%)	1,519 (71.4%)	121 (80.1%)	<0.05
Exercise (≥ 1/week) (n, %)	1,035 (45.4%)	949 (44.6%)	86 (57.0%)	<0.01
Diabetes mellitus (n, %)	40 (1.8%)	31 (1.5%)	9 (6.0%)	<0.001
Hyperlipidemia (n, %)	88 (3.9%)	69 (3.2%)	19 (12.6%)	<0.001
Family history of hypertension (n, %)	317 (13.9%)	291 (13.7%)	26 (17.2%)	0.23
Heart rate (beats/min)	61 ± 10	61 ± 10	62 ± 10	0.06
Systolic blood pressure (mmHg)	117 ± 9	116 ± 9	127 ± 7	<0.001
Diastolic blood pressure (mmHg)	74 ± 7	73 ± 7	82 ± 5	<0.001
baPWV (cm/s)	1,301 ± 142	1,293 ± 137	1,412 ± 168	<0.001
LDL-cholesterol (mg/dL)	127 ± 31	127 ± 31	126 ± 32	0.68
HDL-cholesterol (mg/dL)	56 ± 14	56 ± 14	54 ± 15	0.09
Triglyceride[a] (mg/dL)	104 (73–150)	103 (73–149)	115 (86–169)	<0.01
Glucose (mg/dL)	93 ± 17	93 ± 16	100 ± 23	<0.001

baPWV Brachial-ankle pulse wave velocity, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Unless indicated otherwise, data are expressed as the mean ± standard deviation (SD)

[a] Triglyceride is expressed as a median and interquartile range (IQR) due to its skewed distribution

(95% CI 5.24–23.29, $P < 0.001$, P for trend <0.001) and the full adjusted OR was 2.70 (95% CI 1.18–6.17, $P < 0.05$, P for trend = 0.01).

Discussion

The results reported here clearly show that baPWV was a significant and independent marker to predict incident hypertension among our study cohort of Japanese normotensive male subjects and that baPWV values >1,380 cm/s

Table 2 Odds ratios and 95% confidence interval of the relationship between brachial-ankle pulse wave velocity and incident hypertension by multiple logistic regression analysis

Model	Odds ratio	95% CI	P value
Model 1	2.16	1.80–2.60	<0.001
Model 2	1.98	1.69–2.31	<0.001
Model 3	1.45	1.17–1.79	<0.01

CI confidence interval

Odds ratio was indicated by a 1 SD (142 cm/s) increase of baPWV values

Model 1 is adjusted for age; Model 2, model 1 plus adjustments for body mass index, smoking, alcohol, exercise, diabetes mellitus, hyperlipidemia, family history of hypertension, heart rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and glucose; Model 3, model 2 plus adjustments for systolic blood pressure

was a high risk factor for the development of hypertension during the 3-year follow-up.

The development of hypertension in normotensive subjects is associated with gender and advancing age [6]. Within the framework of the Framingham study, Vasan et al. [17] demonstrated that over a 4-year period elderly patients with high-normal and normal blood pressure were prone to develop incident hypertension. However, the prediction of future incident hypertension from blood pressure values alone have proved difficult [18]. Previous studies have found that the increased arterial stiffness could be useful markers to predict the development of hypertension [6, 7, 10, 19]. In the Atherosclerosis Risk in Communities (ARIC) study of normotensive subjects, Liao et al. [7] demonstrated that an increase in arterial stiffness of the left common carotid artery measured by high-resolution B-mode ultrasonography was associated with a 15% greater risk for the occurrence of hypertension, independent of conventional risk factors, including baseline blood pressure values. Based on results on normotensive subjects followed for 4 years, Dernellis et al. [20] reported that the arterial stiffness markers, such as aortic strain, destensibility, and the stiff index (β), evaluated by M-mode echocardiography using a technique of polynominal regression analysis could be a predictor of incident hypertension after adjustment for conventional risk factors [6]. The findings in our study are in agreement with these previous studies. The significance of our study is that baPWV was found to be an independent predictor of future

Table 3 Baseline characteristics of the study subjects stratified by the quartiles of baPWV values

Baseline characteristics	Quartile 1: ≤1,204 cm/s ($n = 573$)	Quartile 2: 1,205–1,288 cm/s ($n = 569$)	Quartile 3: 1,289–1,380 cm/s ($n = 568$)	Quartile 4: ≥1,381 cm/s ($n = 568$)	P for trend
Age, years (n)	44 ± 6	45 ± 6	47 ± 6	48 ± 6	<0.001
Body mass index (kg/m^2)	23.4 ± 2.6	23.5 ± 2.7	23.9 ± 2.9	23.8 ± 2.8	<0.01
Smoking (yes) (n, %)	291 (50.7%)	294 (51.7%)	281 (49.5%)	298 (52.5%)	0.77
Alcohol (yes) (n, %)	404 (70.5%)	417 (73.3%)	392 (69.0%)	427 (75.2%)	0.09
Exercise (≥1/week) (n, %)	288 (50.2%)	250 (43.9%)	266 (46.8%)	231 (40.7%)	<0.01
Diabetes mellitus (n, %)	1 (0.2%)	6 (1.1%)	10 (1.8%)	23 (4.0%)	<0.001
Hyperlipidemia (n, %)	15 (2.6%)	13 (2.3%)	25 (4.4%)	35 (6.2%)	<0.01
Family history of hypertension (n, %)	58 (10.1%)	87 (15.3%)	81 (14.3%)	91 (16.0%)	<0.05
Heart rate (beats/min)	58 ± 8	60 ± 9	61 ± 10	65 ± 11	<0.001
Systolic blood pressure (mmHg)	110 ± 8	115 ± 8	118 ± 9	123 ± 8	<0.001
Diastolic blood pressure (mmHg)	69 ± 7	73 ± 7	75 ± 7	79 ± 6	<0.001
LDL-cholesterol (mg/dL)	125 ± 31	125 ± 31	128 ± 30	128 ± 33	0.19
HDL-cholesterol (mg/dL)	57 ± 14	56 ± 14	56 ± 14	56 ± 14	0.22
Triglyceride[a] (mg/dL)	90 (66–130)	101 (70–150)	108 (76–151)	120 (84–167)	<0.001
Glucose (mg/dL)	89 ± 10	92 ± 13	93 ± 14	99 ± 25	<0.001

Unless indicated otherwise, data are expressed as the mean ± standard deviation (SD)

[a] Triglyceride is expressed as a median and interquartile range (IQR) due to its skewed distribution

Table 4 Odds ratios and 95% CI for incident hypertension among quartiles of baPWV values

	Quartile 1: ≤1,204 cm/s	Quartile 2: 1,205–1,288 cm/s	Quartile 3: 1,289–1,380 cm/s	Quartile 4: ≥1,381 cm/s
Cases/subjects	8/573	24/569	37/568	82/568
Model 1				
Odds ratio	1.0	3.03	4.69	11.05
95% CI		1.35–6.81	2.16–10.20	5.24–23.29
P value		< 0.001	< 0.001	< 0.001
			P for trend < 0.001	
Model 2				
Odds ratio	1.0	3.03	4.42	10.16
95% CI		1.34–6.88	2.01–9.74	5.15–22.29
P value		< 0.001	< 0.001	< 0.001
			P for trend < 0.001	
Model 3				
Odds ratio	1.0	1.68	1.73	2.70
95% CI		0.72–3.91	0.76–3.95	1.18–6.17
P value		0.23	0.20	< 0.05
			P for trend = 0.01	

Models 1–3 are as described in footnote to Table 2

hypertension. It should be noted that unlike the echocardiographic methods used in previous studies, baPWV could become the most widely used conventional index of arterial stiffness.

PWV can be used as a predictor of cardiovascular events [21–28]. The carotid–femoral PWV measurement has been used as a conventional and common procedure [29]. baPWV measurements have recently been widely applied using a procedure in which pressure cuffs are wrapped around the brachial artery. In comparison with carotid–femoral PWV, baPWV can be widely applied during routine medical examinations because its measurement is simple and does not require specialized and highly technical equipment and expertise [12, 30]. The measurements have been reported to be valid and reproducible and easier to perform than other noninvasive automatic procedures [11, 31, 32]. The baPWV values have been found to be correlated with intima-media thickness of the carotid artery and closely associated with aortic PWV, an index of central arterial stiffness [11, 12]. In agreement with the results reported here, Yambe et al. [19] found that baPWV was predictive of progression to hypertension in subjects with high-normal blood pressure. However, these researchers had excluded subjects with dyslipidemia, diabetes mellitus, and fasting plasma glucose >125 mg/dL and, consequently, the results may not be applicable to a normotensive general population. This is an important difference between our study and that of Yambe et al. [19].

There are a number of possible explanations of how high baPWV values could predict the incident hypertension. Aortic stiffness can be evaluated by the measurement of baPWV [14]. Stefanadis et al. [33] demonstrated that aortic stiffness was a cause of the premature return of reflected waves in late systole, resulting in increasing central aortic pressure; it was also closely associated with increased afterload. Thus, the elevation of afterload developed into hypertension. Wilkinson et al. [34] have suggested that nitric oxide plays an important role in the development of arterial stiffness as well as hypertension because nitric oxide released from the endothelium cells can alter vascular tone, cell growth and angiotensin receptors. Kameyama et al. [35] demonstrated that the inhibition of nitric oxide synthesis inhibition increased PWV values and, importantly, that their increase preceded the observed vascular structural changes in a rat model. These findings suggest that baPWV values increase as a result of decreases in nitric oxide synthesis and that the latter may be involved in the development of incident hypertension.

There are several limitations to our study that should be acknowledged. First, baPWV is an indirect marker of increased arterial stiffness or decreased arterial compliance, and we did not examine the structural changes of arterial wall using ultrasound technology in our study. Second, the constraints of our study did not allow us to determine the pathophysiological mechanisms linking increased arterial stiffness and the development of hypertension. Third, the identification of hypertension was performed twice (at the beginning of the study and at the end of the 3-year follow-up), and we were unable to examine detailed information on blood pressure, such as variations in blood pressure, during the follow-up period. Fourth, our study subjects were all from a single local government agency, and caution is recommended when applying these results to the general population.

The major strength of our study is that we were able to demonstrate in a Japanese normotensive male study cohort that high baPWV values were closely associated with incident hypertension and that specific baPWV values were associated with a high risk of future incident hypertension. Many previous studies have demonstrated the relationship between incident hypertension and arterial stiffness based on baPWV values [6, 7, 10, 19], but these have not provided the appropriate baPWV values for incident hypertension.

In conclusion, Our results demonstrate that baPWV has the potential to be a significant and independent predictor for the development of hypertension in Japanese normotensive male subjects. They also suggest that baPWV could potentially be a useful and conventional screening method to identify normotensive subjects at a higher risk who could be a target for interventions aimed to prevent and delay the onset of hypertension.

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