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Reference value of brachial-ankle pulse wave velocity for the eastern Chinese population and potential influencing factors

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Abstract

The present study was conducted to obtain reference values for brachial-ankle pulse wave velocity (baPWV) and to evaluate influencing factors of baPWV according to gender. Using automatic devices, baPWV was measured simultaneously in 2095 subjects. A total of 647 healthy subjects, none of whom presented atherosclerotic risk factors, were analyzed in the present study. Two different statistical methods were used to obtain reference values for baPWV according to subject gender and age. The association between baPWV value and gender, as well as other features, were analyzed. For male subjects, multiple stepwise analysis showed that age, systolic blood pressure (SBP), heart rate (HR), and plasma levels of triglycerides (TG) were independent predictors of baPWV. For female subjects, age, SBP, HR, and plasma levels of uric acid (UA) were independent predictors of baPWV. In male subjects, the upper limits of baPWV values were 1497.43/1425.00, 1518.67/1513.25, 1715.97/1726.50, 1925.20/1971.90, and 2310.18/2115.00 cm/s, obtained using two different statistical methods for the age ranges of 30-39, 40-49, 50-59, 60-69, and 70 and older, respectively. For females, the upper limits of baPWV values were 1426.70/1411.13, 1559.15/1498.95, 1733.50/1739.00, 1958.63/1973.78, and 2720.80/2577.00 cm/s for the age ranges of 30-39, 40-49, 50-59, 60-69, and 70 and older, respectively. Aging is the most important influencing factor for baPWV value and its effect is more prominent in females. The reference values of baPWV according to age and gender may be useful for the clinical diagnosis and preventive therapy of cardiovascular diseases.

Key words: Pulse wave velocity; Reference value; Age; Gender; Influencing factor

Introduction

Arteries are channels that transmit blood at high pressure to peripheral vascular beds (1). Arterial elasticity dysfunction is an important marker of cardiovascular risk and arterial stiffness plays a key role in the pathophysiology of the cardiovascular system (2-4). Increased arterial stiffness parallels structural changes in the medial layer of the elastic arteries (mainly aorta and major arterial conduits), and is largely the result of progressive elastic fiber degeneration. An increase in stiffness related to arterial wall composition occurs with aging, and is accelerated in patients with hypertension (5,6).

In recent years, great emphasis has been placed on the role of arterial stiffness in the development of cardiovascular (CV) diseases. Arterial stiffness has an important, independent predictive power with respect to cardiovascular mortality, coronary events and several atherosclerotic diseases (2,7). Measurement of pulse wave velocity (PWV) in human subjects has been proposed as one method to diagnose and evaluate distensibility of large arteries and to assess arterial stiffness. PWV, which is inversely related to arterial wall distensibility, offers a simple and potentially useful approach for evaluating cardiovascular disease (8,9). In-depth studies regarding PWV have been conducted and PWV is now considered to be an independent predictor of CV risk and prognosis. PWV not only reflects systemic arteriosclerosis but also relates to cardiovascular risk factor (10), and ischemic heart disease in type II diabetes mellitus (10,11). The aortic PWV is the “gold standard” marker for measuring arterial stiffness, and is widely used to estimate vascular stiffness and “vascular health” (1). Carotid-femoral PWV is widely used, although complicated techniques are required to obtain an accurate pulse wave

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measurement (2).

Brachial-ankle pulse wave velocity (baPWV) has been developed as a simple noninvasive index of arterial stiffness (12-15) and has been reported to be correlated with carotid-femoral PWV (12,15). The baPWV measurement is a reflection of the flexibility of the aorta and medium arteries. This method is simple and reproducible, saves time, and is also suitable for large-scale population screening and follow-up. Therefore, in order to adopt baPWV for routine clinical use and render it a powerful tool for early diagnosis of atherosclerosis in medical institutions, it is vital to determine reference value of baPWV in healthy subjects. The purpose of the present study was to investigate major influencing factors of baPWV in healthy eastern Chinese people and to determine the reference values of baPWV in healthy people in different age groups and gender.

Material and Methods

Study population

A total of 2095 consecutive subjects ranging in age from 30 to 85 years, from the Pudong New Districts of Shanghai, China, were enrolled in this study between July and August 2009. Informed consent was obtained from all subjects. We analyzed the cross-sectional epidemiological data at the end of the study. Of the 2095 volunteers, 647 were considered to be healthy and did not present any atherosclerotic risk factors. These subjects were separated according to gender and age for analysis of baPWV. A 'healthy subject' was defined by the following criteria: blood pressure <140/90 mmHg, fasting blood glucose (FBG) <6.1 mM, total cholesterol (TC) <5.9 mM, triglycerides (TG) <1.70 mM, male enzymatic uric acid (UA) <428 µM, female enzymatic UA <357 µM, body mass index (BMI) <25, no medication, no history of CV diseases, and no history of smoking (12,16).

Measurement of baPWV

baPWV was measured in 2095 subjects using an automated device (Model BP203RPE-II [VP-1000], Omron, Japan). baPWV, systolic blood pressure (SBP), diastolic blood pressure (DBP), electrocardiogram, and heart sounds were recorded simultaneously. None of the participants took any medications on the day of the examination. Measurements were performed in the supine position. Waveforms were obtained from volume plethysmographic sensors in cuffs on the right brachium and both ankles. The instrument automatically recorded the time intervals (Tba) between the wave at the right brachium and at both ankles. The distance between the sampling points of baPWV was calculated using the following equation: baPWV = (La - Lb) / Tba, where Lb represents the length from the suprasternal notch to the right brachium (Lb) = 0.2195 x height (cm) - 2.0734, and La represents the length from the suprasternal notch to the ankle (La) = 0.8129 x height (cm) + 12.328.

The baPWV was calculated as the distance between recording sites measured over the surface of the body, divided by the time interval of the pressure waves between the feet (17,18). This device automatically and simultaneously measures bilateral baPWV and brachial and ankle blood pressures. In our analysis, we used the mean value of the bilateral baPWV, and left brachial blood pressure.

Laboratory measurements

Fasting venous blood samples were drawn, and TC, TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), plasma levels of UA, high sensitivity C-reactive protein (hs-CRP), FBG, and hemoglobin A1c (HbA1c) were measured using standard methods.

Statistical analysis

Continuous variables are reported as means ± SD or median (quartile range) according to the characteristics of the data. The Kolmogorov-Smirnov test was applied to assess data distribution. Differences between variables were compared using the independent samples *t*-test, while the Mann-Whitney U-test was used to assess data that were not normally distributed. Linear correlations were determined using Spearman's rank-order correlation coefficient, and stepwise multiple regression analysis was performed to determine factors associated with baPWV. Potential risk factors, including age, blood pressure, heart rate, serum lipid, FBG, plasma level of UA, hs-CRP, and BMI were assessed in multiple analyses. The average values of the right and left baPWV were used in the statistical analysis. The arctan transformed baPWV value was used to determine the reference range of baPWV, and the upper limit was calculated by adding the mean value to +1.64 x SD, followed by the application of tangent transformation. The percentile method was also used to deduce the reference range of baPWV. Statistical calculations were performed using the SPSS software, version 14.0 (SPSS, USA). P values ≤0.05 were considered to be statistically significant.

Results

Clinical characteristics

The clinical characteristics of the healthy subjects are shown in Table 1. The total number of subjects consisted of 702 men and 1393 women. The male subjects had a mean age of 58.12 ± 10.86 years (range, 30-87 years) and female subjects had a mean age of 57.14 ± 9.25 years (range, 30-88 years). There was no significant difference in pulse pressure, ankle-brachial index, BMI, hs-CRP, or HbA1c (%) between genders. In contrast, males had higher values with respect to age, SBP, DBP, mean blood pressure, baPWV, height, weight, waist, TG, UA, TC/HDL-C ratio, and FBG (male *vs* female, $P < 0.05$). In females, TC, HDL-C, and LDL-C values were significantly higher (female *vs* male, $P < 0.05$).

BaPWV and influencing factors

The results of step-wise multiple regression analysis

between baPWV and other clinical variables revealed that, in males, age, SBP, heart rate, and TG were significant variables and, in females, age, SBP, heart rate and UA were positively associated with baPWV (Table 2).

The relationship between age and baPWV by gender

The Mann-Whitney U-test was used to analyze baPWV values according to gender. The results revealed that the baPWV values differed significantly between genders (Z = -2.781, P = 0.005). The Kruskal-Wallis H-test was used to compare baPWV values among different age groups by gender, and the results showed that the values of baPWV among different age groups were also statistically significant (H = 49.810, P = 0.000 in male versus H = 120.120, P = 0.000 in female). The changes in age and baPWV for both males and females are displayed in Figure 1. Lines within boxes represent median values. The upper and lower boundaries of the boxes indicate the 25th and 75th percentiles, and bars above and below the boxes indicate minimum and maximum values, respectively.

In the estimation of the regression curve (the relationship between age and baPWV) both genders demonstrated a quadratic curve: baPWV (male) = 0.1354 x age^2 - 3.8846 x age + 1203.1 (R^2 = 0.2736, P < 0.001; Rs = 0.487, P < 0.001); baPWV (female) = 0.2237 x age^2 - 9.6129 x age + 1220.8 (R^2 = 0.2642, P < 0.001; Rs = 0.549, P < 0.001). In addition to the value of the standardized coefficient in multiple regression analysis, the Spearman correlation coefficient between age and baPWV also showed that the effect of age on baPWV was greater in females than that in males.

Determination of reference values of baPWV by two kinds of methods

In order to obtain reference values for baPWV, we applied the percentile method and arctan transformation method to the different age groups of both genders. The results are listed by gender in Table 3. In contrast to the female population, the arctan transformation method revealed that healthy male subjects had a higher baPWV value when less than 40 years of age. Similarly, the percentile method revealed that healthy male subjects had a higher baPWV value when less than 50 years of age.

Discussion

The change in arterial function and structure is the main implication for clinical CV events. To date, the methods for evaluating arterial function are very limited; therefore, the clinical significance of noninvasive evaluation of early vascular diseases has attracted more attention. Increasing arterial stiffness is a pathological state of vascular damage, and is closely associated with atherosclerotic cardiovascular diseases, such as coronary artery disease (19,20). Pulse wave velocity is widely used as an indicator of arterial stiffness, and it has been shown that PWV is also

Table 1. Clinical characteristics of male and female participants of this study (N = 2095).

Variables	Male (N = 702)	Female (N = 1393)
Age (years)	58.12 ± 10.86	57.14 ± 9.25*
SBP (mmHg)	136.29 ± 20.58	132.36 ± 22.47*
DBP (mmHg)	77.99 ± 11.89	74.52 ± 11.52*
MBP (mmHg)	97.43 ± 13.72	93.80 ± 17.65*
PP (mmHg)	58.30 ± 14.59	57.84 ± 13.70
baPWV (cm/s)	1556.25 (431.00)	1482.00 (420.00)*
ABI	1.11 ± 0.08	1.10 ± 0.08
Height (cm)	168.11 ± 6.16	157.35 ± 5.69*
Weight (kg)	68.82 ± 10.10	59.50 ± 9.14*
BMI (kg/m^2)	24.32 ± 3.10	24.03 ± 3.41
Waist (cm)	88.80 ± 8.86	84.65 ± 8.78*
Laboratory parameters		
TC (mM)	4.90 ± 0.94	5.34 ± 0.97*
TG (mM)	1.94 ± 1.60	1.71 ± 1.20*
HDL-C (mM)	1.16 ± 0.29	1.37 ± 0.32*
LDL-C (mM)	2.88 ± 0.79	3.22 ± 1.12*
UA (μM)	366.67 ± 78.42	290.32 ± 67.94*
hs-CRP (g/L)	2.06 ± 2.85	2.10 ± 3.30
T/HR	4.42 ± 1.29	4.06 ± 1.09*
FBG (mM)	5.52 ± 1.46	5.35 ± 1.25*
HbA1c (%)	6.02 ± 2.22	5.95 ± 1.64

Data are reported as means ± SD, except for baPWV. SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure; baPWV = brachial/ankle pulse wave velocity; ABI = ankle-brachial index; BMI = body mass index; TC = plasma levels of total cholesterol; TG = plasma levels of triglycerides; HDL-C = plasma levels of high-density lipoprotein cholesterol; LDL-C = plasma levels of low-density lipoprotein cholesterol; UA = plasma levels of uric acid; hs-CRP = high sensitivity C-reactive protein; T/HR = TC and HDL-C ratio; FBG = fasting blood glucose; HbA1c = hemoglobin A1c. *P < 0.05, compared to males (independent samples t-test).

Table 2. Step-wise multiple regression analysis using the baPWV of healthy subjects as the dependent variable.

Variables	Standardized coefficients	t-values	P	R^2
Males (N = 194)				0.434
Age	0.457	7.963	<0.001	
SBP	0.316	5.462	<0.001	
HR	0.183	3.207	<0.001	
TG	0.121	2.120	0.035	
Females (N = 453)				0.528
Age	0.458	12.706	<0.001	
SBP	0.350	9.703	<0.001	
HR	0.209	6.109	<0.001	
UA	0.083	2.441	0.015	

SBP = systolic blood pressure; HR = heart rate; TG = plasma levels of triglycerides; UA = plasma levels of uric acid.

an important predictor of risk and prognosis of CV disease (2,12,14,15,21). Considering the relationship between flow-mediated dilation of the brachial artery, carotid intima-media thickness and PWV, the combination of these measures may be of clinical significance (22).

Some studies have demonstrated that conventional atherosclerotic risk factors such as smoking, obesity, diabetes mellitus, and dyslipidemia influence PWV (23-26). In order to eliminate these confounding variables, the present study was carried out on a population of 'healthy subjects' who did not present any atherosclerotic risk factors. The result of the present study showed that the older the subject, the greater the upper limit value of baPWV, especially in people over 60 years. Males had a higher average and upper limit values than females at less than 50 years of age. Above 50 years of age, females had higher baPWV. It was also reported that marked arterial stiffness was fitted with non-linear quadratic equation over 55 years of age (27). Although the present data did not meet normality requirements sufficient for common data transformation (P = 0.000), the data met the requirement of normality for arctan transformation (P = 0.200). In the present study, the normal distribution method via arctan transformation and the percentile method were used to determine the reference value of baPWV in different age groups by gender, and the upper limit of normal distribution and 95th percentile were considered for the formulation of said value. The normal value of baPWV will primarily aid in determining the degree of atherosclerosis, and in facilitating primary screening of potential cardiovascular and cerebrovascular diseases. Therefore, it is necessary to quickly and accurately detect patients with increased arterial stiffness in order to avoid or delay the occurrence and development of cardiovascular and cerebrovascular events.

For the elderly, who have no clinical symptoms of cardiac or cerebrovascular disease, increasing age induces pathological changes in the structure and function of the arterial wall. Age, blood pressure and other unknown factors are causes of increased arterial stiffness (16,28,29). The present study revealed that baPWV increased with age in both males and females, with no exception. In recent years, clinical studies have shown that decreased aortic compliance was an independent risk of CV disease mortality. In the present study, multivariate analysis demonstrated that age was a more important determinant of baPWV in females than in males independent of blood pressure variables. Although we could not confirm the menopausal status of each individual, the results in Table 3 show that menopause was an important factor influencing arterial stiffness in healthy females. Considering that levels of estrogens and androgens in females and males fluctuate with age, it is possible that the influence of age on the arterial tree may have contributed to this result. We also observed that the baPWV of both males and females was positively correlated with heart rate. Despite this result, an inherent correlation between the increase in heart rate and the reduction of arterial elasticity is not clear. A high heart rate shortens the time available for recoil, which can lead to arterial stiffening. Epidemiological and clinical studies have confirmed a relationship between increased serum uric acid and the

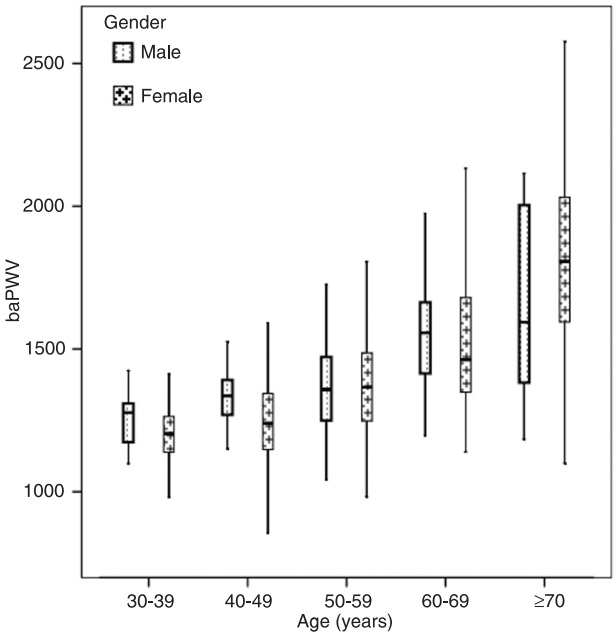

Figure 1. Box plots showing the median and dispersion of brachial-ankle pulse wave velocity (baPWV) distribution according to different age groups by gender.

Table 3. Reference brachial-ankle pulse wave velocity (baPWV) values for men and women.

Age (years)	Arctan transformed		Percentile	N
	Arctan (baPWV)	baPWV (cm/s)	baPWV (cm/s)	
Males (N = 194)				
30-39	1.570129	1497.43	1425.00	15
40-49	1.570138	1518.67	1513.25	36
50-59	1.570214	1715.97	1726.50	79
60-69	1.570277	1925.20	1971.90	51
≥70	1.570401	2310.18	2115.00	13
Females (N = 453)				
30-39	1.570095	1426.70*	1411.13	34
40-49	1.570155	1559.15*	1498.95	98
50-59	1.570219	1733.50	1739.00	236
60-69	1.570286	1958.63	1973.78	66
≥70	1.570429	2720.80	2577.00	19

*P < 0.001, compared to males (Mann-Whitney U-test). The 95th percentile was used to define the upper limits.

incidence and mortality of CV disease (30). Hyperuricemia is an independent indicator of carotid-femoral pulse wave velocity (cfPWV) and carotid-radial pulse wave velocity. We observed that baPWV in females correlated positively with UA, and, in males, a correlation between baPWV and TG was observed.

Recently, with the development of noninvasive measurement techniques and the increased incidence of cardiovascular diseases, PWV for noninvasive measurement, which can effectively reflect arterial stiffness, has become a hot topic in cardiovascular research. cfPWV is the most studied technique, and its reproducibility and validity have been well verified. However, cfPWV can only reflects the flexibility of aortic arteries, and the measurement method is relatively complicated, while baPWV reflects the elasticity of both the aorta and middle arteries and the measurement method is simple and time-saving. Based on these criteria, baPWV has greater application prospects compared to cfPWV. The detection of PWV can help identify early changes in vascular structure and function in a high-risk cohort with cardiovascular diseases. The assessment of the damage in arterial structure and function is of great value in determining high-risk patients and judging the efficacy of treatments.

This study showed that there was a significant independent correlation between baPWV and age, SBP, heart rate, and TG in men, while there was a significantly independent correlation between baPWV and age, SBP, heart rate, and UA in women. These results suggest that baPWV may be used to identify the development of atherosclerosis and the risk of CV diseases, and offer guidance for treatment.

Aging is the most important influencing factor of baPWV, and this effect is more prominent in females. The reference values of baPWV according to gender and age may be valuable for clinical treatment and preventive medicine in cardiovascular disease.

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