ISSN 2320 7159

INTERNATIONAL JOURNAL OF MEDICAL RESEARCH

ORIGINAL ARTICLE

Association between Whole Blood Viscosity and Arterial Stiffness in Overweight and Obese Adults

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ARTICLE INFO

doi: 10.5455/ijmr.20140805121010

Keywords:
Whole Blood Viscosity;
Obese;
Brachial-ankle Pulse Wave;
Arterial Stiffness

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ABSTRACT

Introduction: Obesity plays a key role in the development of cardiovascular diseases. The brachial-ankle pulse wave velocity (baPWV) is an indicator for early atherosclerotic changes. Recently, the effect of changed blood rheology on atherosclerosis has received attention. Our objective in this report is to examine the association of rheological parameters with baPWV in overweight and obese adults.

Methods: In this cross-sectional study, we determined the relationship between rheological parameters and baPWV in 964 subjects (560 men and 404 women) in a general health examination.

Results: Compared with control subjects, baPWV levels were increased in overweight and obese adults. Moreover, there was a positive correlation between baPWV and whole blood viscosity (WBV 3 s^{-1}) in overweight and obese subjects after adjusting confounding factors. Stepwise multiple linear regression analysis revealed that WBV (3 s^{-1}) was a significant determinant for increased baPWV ($\beta = 0.161$; $P = 0.003$).

Conclusion: The findings showed that baPWV and WBV (3 s^{-1}) elevated in overweight and obese adults compared with control subjects. In addition, WBV (3 s^{-1}) was independently associated with baPWV after adjusting other cardiovascular risk factors.

INTRODUCTION

The obesity epidemic is a global public health problem. Obesity is a determinant factor in the development of cardiovascular diseases, and is associated with an increased incidence of metabolic syndrome, hypertension, diabetes, stroke, and higher all-cause mortality.[1] Arterial stiffness due to decreased arterial compliance is one of the major signs of vascular aging.[2] Elevated arterial stiffness, an indicator of subclinical atherosclerosis, is linked to myocardial infarction, heart failure, stroke, renal disease, and all-cause mortality.[3] Pulse wave velocity (PWV) reflects the stiffness of central and peripheral muscular arteries and is widely used as an index of arterial stiffness and vascular damage. Brachial-ankle PWV (baPWV) measurement, a simple, noninvasive, and automated measurement method, is closely correlated with aortic PWV.[4] Previous studies stated that increased baPWV is found in metabolic syndrome, cardiovascular diseases, stroke, and renal disease.[5-8]

Altered hemorheological parameters have also been shown to play a key role in atherogenesis. Many car-

diovascular risk factors, including aging, obesity, carotid intima-media thickness, are linked with changes of hemorheological parameters[9-11] Furthermore, increased viscosity has been acknowledged as a significant contributing factor in the development of various chronic diseases such as metabolic syndrome, hypertension, diabetes, ischemic heart disease, and stroke[12-15] A recent study confirmed that whole blood viscosity (WBV) is a predictor of cardiovascular events.

Based on the assumption that both WBV and baPWV are related to cardiovascular disease, we postulated that there would be a close relationship between the level of WBV and baPWV. Therefore, the aim of the study is to examine whether rheological parameters are independently associated with baPWV in overweight and obese adults.

MATERIALS AND METHODS

Study population

The study included 964 persons (560 men and 404 women) who received general health examination from January 2011 to December 2012 from the International Physical Examination and Healthy Center at the Second Affiliated Hospital, Harbin, Heilongjiang, China. Eligible individuals included obese (body mass index (BMI) ≥ 30.0) or overweight (25.0 ≤ BMI ≤ 29.9) males and females, between 30 and 55 years old. Subjects were excluded from the study if they had the diagnosis of hypertension, diabetes mellitus, cardiovascular diseases, sleep apnea syndrome, chronic hepatic or renal disease, infectious diseases, endocrine disorders, and cancer. We also excluded the subjects with significant weight loss or gain (more than 3 kg of self-reported change during the previous 3 months) and any medical treatment. The study protocol was approved by the Ethics Committee of the Second Hospital of Harbin Medical University, with written informed consent obtained from each participant.

Clinical examination

Clinical data including medical history, lifestyle behaviors and medication use were recorded for each participant. Subjects were asked about lifestyle behaviors including cigarette smoking, alcohol consumption, and physical activity. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for 1 year or more. Regular leisure-time physical activity was defined as participation in moderate or vigorous activity for 30 minutes or more per day at least 3 days a week. All the subjects underwent physical examination which included anthropometric and blood pressure measurements. Arterial blood pressure was measured by a mercury sphygmomanometer after the patient had been in a sitting position for 15 minutes. Systolic and diastolic blood pressures were measured twice on the same day and mean values were used in the analysis. Height was measured without shoes by a stadiometer to the nearest millimeter and weight was measured by electronic scales to the nearest 0.1 kg with the participants clothed lightly. BMI was calculated as weight (kg) divided by height (m^2).

Biochemical analyses

Fasting venous blood samples were taken for the analysis. The values included total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), and fasting plasma glucose (FPG). All assays were performed at the Laboratory of Analytical Biochemistry at the Second Hospital of Harbin Medical University, Harbin, using a biochemical analyzer (Modular Analytics, Roche, Mannheim, German). Whole blood viscosity was assayed at shear rates between 3 s^{-1} and 200 s^{-1} corrected hematocrit of 45% at 37℃ using a viscometer (Succeeder SA-9000, Beijing, China). Plasma viscosity was determined by Harkness method and hematocrit was evaluated by microcentrifugation. Plasma fibrinogen concentrations were measured on the Beckman Coulter ACL-TOP analyzer (Instrumentation Laboratory, Lexingtion, MA, USA). Haemoglobin was determined with an autoanalyzer (Sysmex XE-2100, Kobe, Japan). All measurements were conducted within 2h of sampling.

Measurement of baPWV

BaPWV was measured using an automatic device (model MB3000, M&B Electronic Instruments, Beijing, China). The subjects rested in the supine position for 5 min. The baPWV was automatically calculated according to the formula (L/PTT). L is the difference between the length from heart to ankle and the length from heart to brachium. PTT was the pulse transit time between the brachial and tibial arterial waveforms. All measurements were conducted by a single examiner who was blinded to the clinical data. The method was validated in a previous report.[16]

Statistical analysis

Data were presented as median/inter-quartile range (IQR) or mean (SD) for continuous variables, and frequency and percentages for categorical variables. The Chi-square statistical test was used for categorical variables, while one-way ANOVA or Kruskal-Wallis H was used for continuous variables. Correlations between baPWV and WBV (3 s^{-1}) were tested by partial correlation. Stepwise multiple linear regression analysis was performed to assess the correlation between baPWV and WBV (3 s^{-1}). Variables such as TG, HDL, and FPG were logarithmically transformed before statistical analysis to approximate normal distribution. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the SPSS software package version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The clinical and biochemical characteristics of the subjects are shown in Table 1. Age, SBP, DBP, FPG, TC, TG, LDL, baPWV, hematocrit, WBV 3 s^{-1}, WBV 200 s^{-1}, fibrinogen, and plasma viscosity increased gradually as BMI increased. Physical activity and HDL levels decreased gradually as BMI increased. However, sex, smoking status, drinking, and hemoglobin showed no difference.

The means of baPWV in three groups are shown in Fig 1. There was a significant difference in baPWV levels between overweight adults with control subjects (p=0.033, post hoc LSD test). BaPWV levels elevated in obese adults compared with those in control subjects ($p < 0.001$, post hoc LSD test). Moreover, baPWV levels in obese subjects were higher compared to those in overweight subjects ($p = 0.001$, post hoc LSD test).

Table 1: Clinical and biochemical characteristics of subjects.

Variables	Control	Overweight	Obese	*P*-value*
N	324	322	318	
Age (years)	42.1 (6.8)	43.6 (7.6)	43.9 (7.6)	0.004
Sex (male, %)	185 (57.1)	180 (55.9)	195 (61.3)	0.345
BMI (kg/m²)	23.2 (1.4)	27.4 (1.3)	31.5 (1.1)	<0.001
Smoker (n, %)	97 (29.9)	93 (28.9)	112 (35.2)	0.180
Drinking (n, %)	84 (25.9)	91 (28.3)	105 (33.0)	0.131
Physical activity (n, %)	76 (23.5)	52 (16.1)	41 (12.9)	0.001
SBP (mmHg)	117.9 (13.2)	123.6 (10.3)	129.7 (8.0)	<0.001
DBP (mmHg)	76.2 (7.7)	76.2 (6.9)	78.3 (6.5)	<0.001
FPG (mmol/L)	4.60 (4.10-5.05)	4.69 (4.24-5.18)	5.06 (4.67-5.53)	<0.001
TC (mmol/L)	4.51 (0.78)	4.64 (0.77)	5.08 (0.87)	<0.001
TG (mmol/L)	2.21 (1.62-2.89)	2.64 (1.97-3.16)	2.69 (2.24-3.38)	<0.001
HDL (mmol/L)	1.43 (1.17-1.62)	1.38 (1.14-1.56)	1.22 (0.98-1.44)	<0.001
LDL (mmol/L)	2.85 (0.78)	2.92 (0.74)	3.10 (0.60	<0.001
Hemoglobin (g/dL)	126.1 (10.8)	125.1 (10.1)	124.9 (10.9)	0.338
Hematocrit (%)	42.3 (4.3)	43.1 (4.7)	43.3 (3.6)	0.010
Fibrinogen (mg/dL)	329.7 (69.3)	337.9 (69.8)	348.3 (52.9)	0.001
BaPWV (cm/s)	1246.7 (153.6)	1272.9 (156.9)	1312.7 (157.7)	<0.001
WBV 3s^{-1} (mPa.s)	7.50 (0.92)	8.75 (1.03)	10.53 (1.11)	<0.001
WBV 200s^{-1} (mPa.s)	4.46 (0.38)	4.59 (0.35)	4.73 (0.38)	<0.001
PV (mPa.s)	1.60 (0.08)	1.63 (0.08)	1.66 (0.10)	<0.001

Data are expressed as means (SD) or median (inter-quartile range) or percentage.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BaPWV, brachial-ankle pulse wave velocity; WBV, whole blood viscosity; PV, plasma viscosity.

**p* value was calculated by one-way ANOVA test or Kruskal-Wallis *H* or chi-square test.

Table 2: Partial correlation coefficient (*r*) for baPWV in relation to WBV 3s^{-1} levels (mPa.s)**.**

	Control group		Overweight group		Obese group	
	r	P value	r	P value	r	P value
Model 1[a]	0.015	0.789	0.120	0.033	0.148	0.009
Model 2[b]	0.027	0.640	0.230	0.025	0.148	0.009
Model 3[c]	0.034	0.554	0.211	0.042	0.148	0.010

[a] Model 1: adjusted for age, sex, BMI, drinking, smoking status, and physical activity.
[b] Model 2: adjusted for age, sex, BMI, drinking, smoking status, physical activity, SBP, DBP, FPG, TC, TG, HDL, and LDL.
[c] Model 3: adjusted for age, sex, BMI, drinking, smoking status, physical activity, SBP, DBP, FPG, TC, TG, HDL, LDL, hemoglobin, and fibrinogen.

Variables such as TG, HDL, and FPG were logarithmically transformed before statistical analysis. Abbreviations: see to Table 1.

Table 3: Stepwise multivariate linear regression analysis with baPWV (cm/s) as the dependent variable

Variables	β	95% CI	*p*-value
Age (years)	0.098	0.584-3.664	0.007
WBV $3s^{-1}$ (mPa.s)	0.161	4.814-24.025	0.003
SBP (mmHg)	0.094	0.205-2.234	0.019

β, standardized regression coefficients.

BaPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; WBV, whole blood viscosity.

The *p*-value for entry was set at 0.05, and the *p*-value for removal was set at 0.10. Adjusted $R^2 = 0.080$, $p < 0.001$.

TG, HDL, and FPG were log-transformed before statistical analysis.

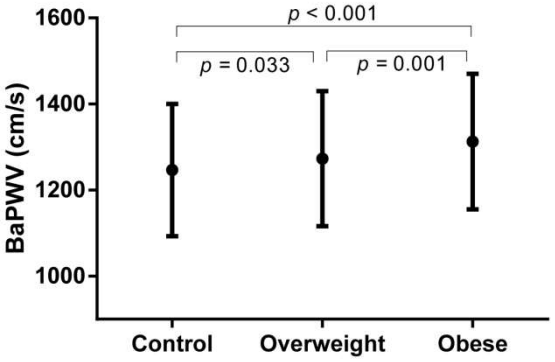

Fig 1: The means of baPWV in the three groups are shown. BaPWV values in control, overweight and obese subjects were 1246.7 (153.6), 1272.9 (156.9), and 1312.7 (157.7) cm/s, respectively.

The partial correlation between baPWV and WBV 3 s^{-1} are summarized in Table 2. No significant correlations were observed between baPWV and WBV 3 s^{-1} in control subjects. However, baPWV statistically correlated with WBV 3 s^{-1} both in overweight and in obese adults. Moreover, the relationship still exists even after adjusting for age, sex, drinking, smoking status, physical activity, SBP, DBP, FPG, TC, TG, HDL, LDL, hemoglobin, and fibrinogen.

Stepwise multiple linear regression analysis was performed to assess the correlation between baPWV and rheological parameters. Fifteen variables including age, BMI, physical activity, SBP, DBP, TC, TG, HDL, LDL, PV, FPG, WBV$3s^{-1}$, WBV$200s^{-1}$, HCT, and fibrinogen entered into the original multivariate model. Our results showed that age, SBP, and WBV (3 s^{-1}) were correlated with baPWV in the model. Notably, WBV (3 s^{-1}) was found to be a significant determinant for increased baPWV ($\beta = 0.161$; $P = 0.003$).

DISCUSSION

In this study, we found that WBV and baPWV levels increased in overweight and obese adults. Furthermore, there was a positive correlation between baPWV and WBV 3 s^{-1} both in overweight and in obese subjects after adjusting confounding factors. Stepwise multiple linear regression analysis revealed that WBV (3 s^{-1}) was a significant determinant for increased baPWV.

Our study indicated that serum WBV at low shear rate has a tight correlation with baPWV in overweight and obese adults. There are several plausible mechanisms for the abnormalities of blood viscosity and the accelerated arterial stiffness. Firstly, excess adipose tissue induces dysregulation in the production of adipokines, which results in a state of low-grade chronic inflammation, as well as insulin resistance and endothelial dysfunction. Furthermore, insulin resistance and metabolic syndrome are associated with hyperviscosity syndrome.[17] In low-shear stress, flow alterations cause reduced shear stress in focal areas, resulting in endothelial remodeling and altered physiological responses.[18] Elevated WBV has been shown to lead to vascular remodeling, altered lipid metabolism, and endothelial inflammation.[19, 20] Also, it has been observed that low-grade chronic inflammation induces vascular damages.[21] Different inflammatory mediators are implicated in the induction of endothelial dysfunction, plaque formation and plaque instability in atherosclerotic disease.[22] A meta-analysis confirmed that obesity is associated with elevated levels of C-reactive protein (CRP), a marker of inflammation and a predictor of cardiovascular risk.[23] Some inflammatory markers, such as CRP, IL-6 and TNF-alpha, are positively correlated with blood viscosity.[15] In addition, increased blood viscosity is linked with metabolic syndrome, hypertension, ischemic heart disease, and stroke, which all are associated with chronic inflammation.[12-15] Finally, obesity is closely associated with hypertension, hypertriglyceridemia, low HDL-cholesterol, and endothelial dysfunction. The accumulation of these risk factors accelerates the progression of atherosclerosis under a state of insulin resistance. Recent studies revealed that insulin resistance is associated with hyperviscosity syndrome.[24, 25] Moreover, a number of studies have reported that WBV is positively correlated with TG concentrations and negatively correlated with HDL-cholesterol.[26, 27] Dyslipidaemia, insulin resistance, and high viscosity accelerate the development of atherosclerosis in a synergistic fashion.

There are several limitations of this study. First, this was a cross-sectional study, so we could not prove the causality of the detected relationships. Second, the study is lacking in information about inflammatory markers linking WBV at low shear rate and baPWV in overweight and obese adults.

In conclusion, our study showed that baPWV and WBV (3 s^{-1}) elevated in overweight and obese adults

compared with control subjects. In addition, WBV (3 s^{-1}) was independently associated with baPWV after adjusting other cardiovascular risk factors. Early detection of abnormal WBV levels at low shear rate should warrant for early search of undetected arterial stiffness in overweight and obese adults.

Acknowledgements

This study was supported by China Postdoctoral Science Foundation (No. 2013M541409) and Technology Foundation for Selected Overseas Chinese Scholar, Ministry of Personnel of China (No. 2013578).

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