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Increased arterial stiffness in stable and severe asthma☆

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Arterial stiffness;
High sensitivity C-reactive protein

Summary
Background: Systemic inflammation is related to disease progression in asthma. The brachial-ankle pulse wave velocity (baPWV) is a marker for early atherosclerotic changes. The aim of this study is to evaluate the baPWV levels in patients with stable and severe asthma.
Methods: We examined baPWV, high sensitivity C-reactive protein (CRP), lung function parameters, and arterial blood gas analysis in patients with asthma and control subjects. 85 stable asthma patients and 85 severe asthmatics were investigated. 85 control subjects matched for age, gender, body mass index (BMI) and smoking status were recruited.
Results: The patients with severe asthma had increased baPWV and CRP compared with the patients with stable asthma and control subjects. Furthermore, baPWV was elevated in stable asthma compared with control subjects. There was a negative correlation between baPWV and forced expiratory volume in 1 s (FEV_1), after adjusting age, gender, BMI and smoking status ($r = -0.414$, $p < 0.001$). Similarly, baPWV was negatively correlated with FEV_1/forced vital capacity (FVC) ($r = -0.431$, $p < 0.001$). Although there was no correlation between CRP and baPWV in patients with stable asthma, CRP was positively correlated with baPWV in patients with severe asthma ($r = 0.229$, $p = 0.039$).

☆ WX.S participated in data collection, data analysis and manuscript preparation. D.J participated in data collection and data analysis. Y.L participated in manuscript preparation and editing. RT.W participated in study design, data analysis and manuscript preparation. All authors read and approved the final manuscript.

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Conclusions: baPWV tends to increase as pathogenic condition aggravated in asthma. In addition, elevated baPWV correlates with impaired lung function. Our observation suggests that baPWV is useful for early detection of subclinical atherosclerosis in asthma.

Introduction

Asthma is an enormous public health problem in USA resulting in considerable burden and cost. Substantial evidence demonstrated asthma is a chronic inflammatory condition with activation of large numbers of immune and inflammatory cells within the airways. Recent studies reported that systemic inflammation is related to disease progression in asthma [1]. Some proinflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor α (TNFα), and C reactive protein (CRP) are elevated in patients with asthma [1—3].

Elevated arterial stiffness, a marker of subclinical atherosclerosis, is associated with myocardial infarction, heart failure, stroke, renal disease, and elevated total mortality [4]. Pulse wave velocity (PWV) reflects the stiffness of central and peripheral muscular arteries and is widely used as an indicator of arterial stiffness and vascular damage. Brachial-ankle PWV (baPWV) measurement, a simple, noninvasive, and automated measurement method, is closely correlated with aortic PWV. Previous studies documented that increased baPWV is linked with metabolic syndrome, cardiovascular diseases, stroke, and renal disease, as well as elevated total mortality [5—8].

Mounting evidence revealed that the patients with asthma are at increased risks of hypertension, pulmonary embolism, coronary heart disease, heart failure, and all-cause mortality [9—12]. However, the changes of baPWV levels in asthma have not been clearly determined.

The purpose of the present study is to evaluate baPWV levels in stable and severe asthma.

Methods

Participants

The study enrolled 255 adults (aged >18 years, 114 men and 141 women) from June 2011 to June 2012. There were 170 patients with asthma and 85 controls without asthma. The severe asthma patients were included consecutively in the department of respiratory, the First Affiliated Hospital. The stable asthma patients and controls were recruited from the International Physical Examination and Healthy Center of the Second Affiliated Hospital. Control subjects were matched for age, gender, and body mass index (BMI), and smoking status. The study protocol was approved by the Ethics Committee of the First and Second Hospital of Harbin Medical University, China. Written informed consent was obtained from study participants.

Clinical examination

All the subjects underwent clinical examination which included anthropometric and blood pressure measurements. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Blood pressure was determined using a mercury-gravity sphygmomanometer in a sitting position after a 15-min resting period. Systolic and diastolic blood pressures were measured twice on the same day and mean values were used in the analysis.

Biochemical measurements

Clinical data including smoking habits, medical history and medication use were recorded for each subject. The whole blood samples were drawn in EDTA-containing tubes after an 8-h overnight fasting and all samples were processed within 30 min after blood collection with an autoanalyzer (Sysmex XE-2100, Kobe, Japan). High sensitivity C-reactive protein (CRP) was measured by the nephelometric method (Dade Behring, Marburg, Germany). An arterial blood sample was assayed with a blood gas analyzer (GEM premier 3000, MA, USA) while the subjects were breathing room air for at least 30 min. Forced expiratory volume in one second (FEV_1) was determined with a spirometer (Jaeger, Wurzburg, Germany) according to the American Thoracic Society criteria. Spirometric measurements were analyzed three times and the best result was used in our study. The inter- and intra-assays coefficients of variation (CVs) of all these assays were below 5%.

Measurement of baPWV

BaPWV was measured using an automatic device (model MB3000, M&B Electronic Instruments, Beijing, China). The baPWV was automatically calculated according to the formula (L/PTT). L is the difference between the length from the heart to ankle and the length from the 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 [13].

Diagnosis and exclusion criteria

Stable and severe asthma was defined according to Global Initiative Strategy for Asthma Management (GINA) guidelines. Exclusion criteria were chronic lung disease other than asthma, coronary heart disease, systemic inflammatory diseases, heart failure, renal failure, and medical treatment with statins, angiotensin converting enzyme inhibitors, and systemic glucocorticoids during the previous 8 weeks.

Statistical analysis

Data were expressed as means $\pm$ SD or median (interquartile range) for continuous variables or percentage for

categorical variables. Group comparisons were conducted using ANOVA test for normally distributed data, Kruskal–Wallis test for non-parametric data and chi-square test for categorical data. *Post hoc* analyses using two-tailed Tukey's HSD were conducted to compare the differences for normally distributed data between the groups. Mann–Whitney *U* test was used to compare the differences for non-parametric data between the groups. Correlations between baPWV and clinical parameters were tested by partial correlation with age, BMI, and smoking as continuous variables and gender as dichotomous variables. CRP was skewed and was normalized by logarithmic transformation. Differences and correlations were considered significant at $P < 0.05$ and all reported *P* values are two tailed. Statistical analyses were conducted with SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

The clinical characteristics of subjects are presented in Table 1. The groups were well-matched with respect to age, gender, BMI and smoking status. The medication with inhaled corticosteroid was more prevalent in asthma group. Significant differences in pulmonary function parameters (FEV_1 and FEV_1/forced vital capacity (FVC)) were observed between the groups. The patients with severe asthma had increased baPWV and CRP compared to the patients with stable asthma and control subjects. Furthermore, baPWV was elevated in stable asthma compared with control subjects.

The partial correlation coefficients of baPWV with laboratory parameters after adjustment for age, gender, BMI and smoking status are reported in Table 2. There was a negative correlation between baPWV and FEV_1, after adjusting age, gender, BMI and smoking status ($r = -0.414$, $p < 0.001$) (Fig. 1). Similarly, there was a negative correlation between baPWV and FEV_1/FVC, after adjusting age, gender, BMI and smoking status ($r = -0.431$, $p < 0.001$) (Fig. 2). Further analysis showed that baPWV was negatively correlated with FEV_1 in severe asthma and baPWV

Table 2 Partial correlation of baPWV with laboratory parameters after adjustment for age, gender, BMI and smoking status.

Variables	baPWV (cm/s)	
	r	*p*-Value
Whole group (asthma + controls)		
CRP (mg/L)	0.375	<0.001
FEV_1 (% predicted)	−0.414	<0.001
FEV_1/FVC (%)	−0.431	<0.001
Severe asthma group		
CRP (mg/L)	0.229	0.039
FEV_1 (% predicted)	−0.277	0.012
FEV_1/FVC (%)	−0.204	0.067
Stable asthma group		
CRP (mg/L)	0.117	0.298
FEV_1 (% predicted)	−0.153	0.174
FEV_1/FVC (%)	−0.237	0.033

BaPWV, brachial-ankle pulse wave velocity; CRP, high sensitivity C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity. CRP was log-transformed for analysis.

Table 1 Clinical and laboratory characteristics in severe and stable asthma patients and control subjects.

Variables	Severe asthma	Stable asthma	Controls	*p*-Value
Number	85	85	85	
Age (years)	40.6 (4.0)	39.8 (4.0)	40.5 (4.4)	0.109
Gender (male, %)	42 (49)	35 (41)	37 (44)	0.539
BMI (kg/m^2)	24.9 (3.0)	25.3 (3.2)	25.2 (2.3)	0.436
Smoker (%)				
Current smoker	12(14)	15 (18)	16 (19)	0.695
Ex-smoker	16 (19)	21 (14)	18 (21)	0.644
Non-smoker	57(67)	49 (58)	51 (60)	0.422
SBP (mmHg)	125.5 (9.5)	123.9 (6.6)	124.6 (7.5)	0.162
DBP (mmHg)	70.1 (5.4)	71.2 (5.9)	69.7 (5.5)	0.395
Medication				
Inhaled Corticosteroids (%)	61 (72)	36 (42)	0	<0.001*
FEV_1 (% predicted)	63.9 (11.4)	77.5 (17.5)	94.4 (6.8)	<0.001
FEV_1/FVC (%)	54.1 (10.6)	71.4 (7.4)	83.9 (7.5)	<0.001
PaO2 (mmHg)	67.4 (8.6)	81.6 (7.7)	87.5 (9.3)	<0.001
$PaCO_2$ (mmHg)	31.6 (5.9)	35.3 (8.3)	39.1 (4.4)	<0.001
Haemoglobin (g/dl)	129.9 (13.3)	132.7 (10.7)	132.7 (12.2)	0.147
CRP (mg/L)	11.8 (8.7–17.8)	8.2 (5.5–11.3)	2.5 (1.9–3.4)	<0.001
BaPWV (cm/s)	1384.2 (111.6)	1364.0 (131.6)	1226.2 (120.3)	<0.001

Data are presented as means (SD) or median (interquartile range) or percentage. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; CRP, high sensitivity C-reactive protein; baPWV: brachial-ankle pulse wave velocity. *p*-Value was calculated by one-way ANOVA test or KruskaleWallis H test or chi-square test. **p*-Value was obtained by comparison of severe and stable asthma using chi-square test.

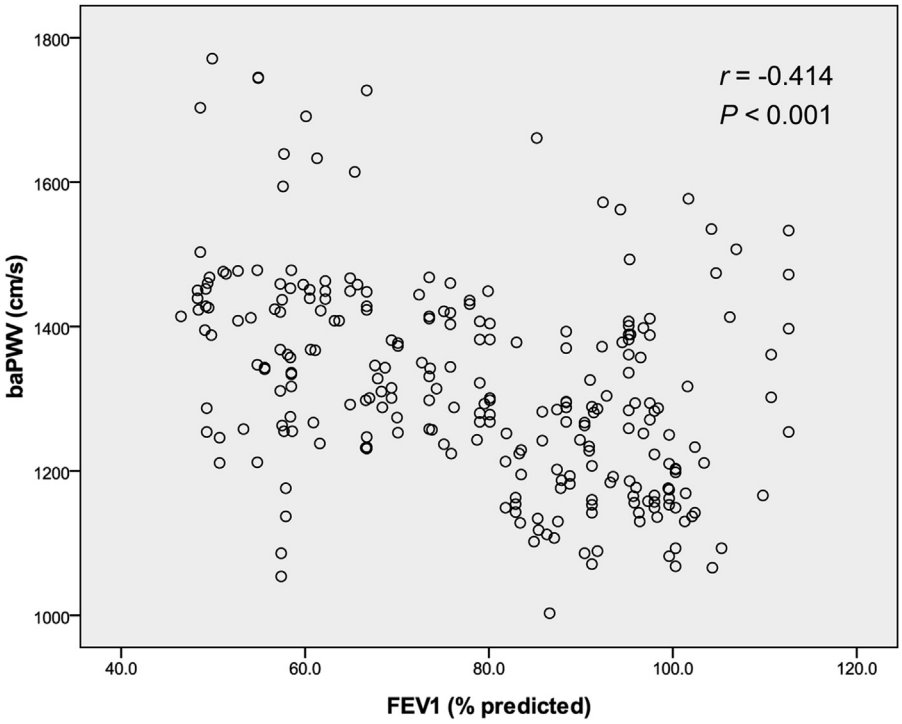

Figure 1 The partial correlation coefficient of baPWV with FEV_1% is presented in Fig. 1 after adjusting for age, gender, BMI and smoking status. BaPWV is negatively correlated with FEV_1%.

was negatively correlated with FEV_1/FVC in stable asthma. Although there was no correlation between CRP and baPWV in patients with stable asthma, CRP was positively correlated with baPWV in patients with severe asthma ($r = 0.229$, $p = 0.039$).

A two-sided Pearson chi-square test was used to analyze the baPWV levels as a correlate of control subjects, stable asthmatics, and severe asthmatics (see Table 3). The results showed a significant difference of baPWV levels in different groups (for the control group *vs.* stable asthma

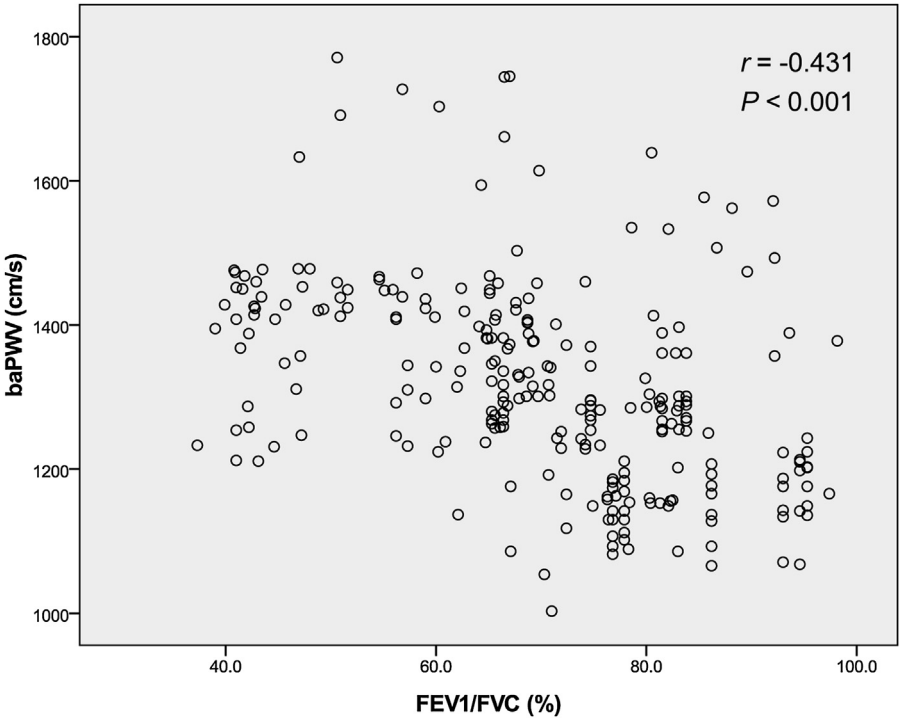

Figure 2 The partial correlation coefficient of baPWV with FEV_1/FVC is presented in Fig. 2 after adjusting for age, gender, BMI and smoking status. BaPWV is negatively correlated with FEV_1/FVC.

Table 3 The analyzed participants distributed according to baPWV quartiles.

	Q1	Q2	Q3	Q4
BaPWV (cm/s)	≤1212	1213–1301	1302–1412	≥1413
Control (*n*)	57	15	5	8
Stable asthma (*n*)*	5	31	35	14
†Severe asthma (*n*)*	2	22	20	41
Total (*n*)	64	68	60	63

BaPWV, brachial-ankle pulse wave velocity. *$P < 0.001$ compared with the control group; †$P < 0.001$ when stable asthma group compared with severe asthma group.

group, $\chi^2 = 73.3$, $P < 0.001$; for the control group *vs.* severe asthma group, $\chi^2 = 83.8$, $P < 0.001$; for stable asthma group *vs.* severe asthma group, $\chi^2 = 20.2$, $P < 0.001$).

Discussion

The main findings of our study are the following: asthmatics had increased baPWV compared to the controls. BaPWV negatively correlated with lung function. Moreover, elevated baPWV was positively related to CRP levels in severe asthma.

There are increased risks of hypertension, pulmonary embolism, coronary heart disease, heart failure, stroke, and all-cause mortality for patients with asthma [9–12]. Systemic inflammation may be the main mechanism for the development and progression of atherosclerosis in asthma. Some proinflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor α (TNFα), and C reactive protein (CRP) are elevated in patients with asthma [3]. Multifactorial complex interactions between platelets, endothelial cells and leukocytes further stimulate production of proinflammatory cytokines and accelerate progression of atherosclerosis [14]. In addition, increased circulating platelet-leukocyte aggregates have been detected in patients with asthma attacks. Recently, a study demonstrated that acute inflammation may cause a significant increase in arterial stiffness [15]. Therefore, evaluating cardiovascular disease risk in asthmatics applying reliable disease markers is of great clinical significance.

Arterial stiffness is a strong predictor of future cardiovascular events and all-cause mortality [16]. The association between increased arterial stiffness and reduced lung volumes has been recently documented [17]. Systemic inflammation mediates the association between lower lung function and cardiovascular disease [18,19]. Our result showed that increased baPWV is positively correlated with CRP only in severe asthma not in stable asthma. These findings are consistent with the idea that the intensity of systemic inflammation rises in severe asthma.

Our result showed that elevated baPWV is negatively correlated with lung function. FEV_1% is a generally accepted surrogate marker of asthma severity. Lower lung function is associated heart failure, stroke, and cardiovascular death [20–22]. Furthermore, reduced FEV_1 is a stronger index of cardiovascular risk than traditional factors such as blood cholesterol [23]. This finding may be partly account for the underlying mechanism linking asthma with increased risk of cardiovascular events.

Age, gender, obesity and cigarette smoking exerted positive effects on baPWV and weight loss and smoking cessation reduced baPWV levels [24–27]. Therefore, we selected the matched patients and ruled out the influence of age, gender, and BMI, and smoking status in our study.

Previous studies have reported that the small arteries elasticity index and systemic vascular resistance are tightly correlated with FEV_1 in asthma [28]. Furthermore, increased carotid atherosclerosis was observed in adult-onset asthma [29]. Our study indirectly confirmed the results using a simple index of atherosclerosis in asthma. Moreover, our study revealed that increased baPWV is positively related to CRP in severe asthma. Consistent with our results, a recent study revealed that reduced lung function is associated with systemic inflammation [18]. Further investigations into the role of baPWV in asthma may be beneficial in the search for therapeutic targets.

The interpretation of this study has some limitations. First of all, our study is a cross-sectional study, so we were unable to infer causality. A prospective study is needed to elucidate the exact association. Secondly, the study is lacking information about the genetic contributions to asthma [30].

Conclusions

Our study shows that baPWV tends to increase as pathogenic condition aggravated in asthma. In addition, elevated baPWV correlates with impaired lung function. Our observation suggests that baPWV is useful for early detection of subclinical atherosclerosis in asthma.

Conflicts of interest

None.

Acknowledgments

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