The Relationship Between the Atherogenic Index of Plasma and Arterial Stiffness in Essential Hypertensive Patients from China: A Cross-Sectional Study

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Abstract

Background: The atherogenic index of plasma (AIP) always remains in a potential association with the arterial stiffness, however, in large hypertensive patient populations, this relation is not fully discovered and needs to be studied in depth. The present analysis thus sought to further explore the association that exists between AIP and arterial stiffness in patients diagnosed with arterial hypertension in China.

Methods: This cross-sectional study analyzed 4744 Chinese individuals with essential hypertension. AIP was defined as the base 10 logarithm of the ratio of plasma of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-c) levels indicates as in molar concentrations. Measurement of arterial stiffness was carried out via brachial-ankle pulse wave velocity (baPWV).

Results: Data were adjusted for potential confounding variables, after which a multivariate linear regression analysis revealed AIP to be positively correlated with baPWV ($\beta = 1.34$, 95% CI: 0.96 to 1.72, $P < 0.001$). When AIP was instead treated as a categorical variable divided into quartiles, this same relationship was observed ($P$ for trend $< 0.001$). We additionally found AIP and baPWV had a stronger positive association in individuals with a body mass index (BMI) $< 24$ kg/m$^2$ ($P$ for interaction $< 0.05$).

Conclusion: AIP and arterial stiffness were positively correlated in essential hypertension patients in China, especially in those with a BMI $< 24$ kg/m$^2$.

Background

Hypertension has been identified as a risk factor associated with high rates of mortality. An estimated 23.2% of adults in China are estimated to suffer from hypertension, which is only controlled in approximately 15.3% of cases [1]. The TROPHY (Trial of Preventing Hypertension) clinical trial has found that vascular changes precede clinical symptoms of cardiovascular changes. Increased arterial stiffness has been reported to be associated with elevated cardiovascular risk [2], and thus, represents a valuable metric to guide the stratification of hypertensive patients based on their cardiovascular risk [3].

Carotid-femoral pulse wave velocity (cfPWV) is presently considered as the gold standard method for assessing arterial stiffness [4], whereas brachial-ankle pulse wave velocity (BaPWV) is similarly validated as a cardiovascular risk marker and is also closely correlated with aortic PWV and cfPWV [5]. As such, BaPWV has been utilized as a valid, reproducible, and routine tool for the non-invasive assessment of patients in clinical studies [6, 7]. As such, BaPWV was used as a metric for arterial stiffness in the present analysis.

The atherogenic index of plasma (AIP) is an easily calculated index value that is based upon circulating lipid levels in a given patient [8]. Relative to individual lipid parameters, AIP is generally superior as it is more strongly correlated with the distribution of small dense low-density lipoprotein (sdLDL) particles [9], which exhibit more pronounced atherogenic activity than do LDL-c particles [10]. Many studies have shown AIP to be a predictor of serious cardiovascular incidents and atherosclerosis in individuals with
coronary arterial disease [11, 12], type 2 diabetes mellitus [13–15] and metabolic syndrome [16, 17], as well as in patients undergoing maintenance hemodialysis [18]. While AIP is thus known to be closely associated with atherosclerosis, its relationship with arterial stiffness is not as well defined. Indeed, only a few studies to date have assessed the association between AIP and arterial stiffness in hypertensive patients. Choudhary et al. found that AIP was directly and independently correlated with arterial stiffness in 615 Finnish patients of hypertension [19], while Si et al. identified a putative positive correlation between AIP and BaPWV when analyzing 380 Chinese hypertensive patients [20], although their study had a limited sample size and failed to effectively adjust for potential confounding variables.

As such, this study was designed for evaluating the association between AIP and arterial stiffness in a large real-world population of hypertensive Chinese patients.

**Methods**

**Participants**

All subjects in the present study were participants in an H-type hypertension Registry Study (Registration number: ChiCTR1800017274) conducted in China from March 2018 to August 2018 in Wuyuan, Jiangxi Province, China. The established standards of inclusion or exclusion as well as the data collection approaches related to this study have been described previously [21]. Briefly, this was a real-world observational study of adults over 18 years of age with hypertension as defined by diastolic blood pressure (DBP) ≥ 90 mmHg and/or systolic blood pressure (SBP) ≥ 140 mmHg, or by the use of antihypertensive agents.

Of the eligible patients, 5,233 completed baPWV measurements and were enrolled in the current study. However, 133 patients with ABI < 0.9 were excluded from the study [6], 103 individuals with atrial fibrillation [6], 168 patients taking lipid-regulating medications, and 85 individuals with triglyceride levels ≥ 500mg/dl [22]. In total, 4744 individuals were considered eligible for the final assessment (Fig 1). The study got approval from the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, and was also consistent with the Declaration of Helsinki. Patients participating in this study provided their written informed consent.

**Clinical data collection**

For each patient, demographic characteristics including age, sex, lifestyle (smoking status, drinking status, and labor intensity) medical history (including atrial fibrillation [AF], stroke, diabetes mellitus, and coronary artery disease), and medication usage (including antihypertensive, lipid-lowering, antiplatelet agents, and hypoglycemic). AF was diagnosed based on a medical history and through resting supine standard 12-lead surface electrocardiograms (25 mm/s, 10 mm/mV).

Anthropometric measurements for each participant including weight, waist circumference, SBP, DBP, and heart rate (HR) were obtained by researchers. A validated non-invasive electronic oscillometric device
(Omron; Dalian, China) with an appropriate cuff size for the upper arm was used to take four consecutive BP measurements (with a time interval of 1-2 min), with the mean values from the three final recordings being used for analytical purposes to decrease the impact of reactivity on BP. BMI was determined as follows: \( \text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 (m^2)} \). Diagnosis of incident diabetes was defined as fasting glucose >7.0mmol/l, and/or self-report diabetes during the follow-up period. All research staff involved in this study underwent identical training to ensure consistency.

**Laboratory assay**

Venous blood specimens were obtained from all patients following a 12 h minimum overnight fasting and were stored at 4°C. Plasma total homocysteine, low-density lipoprotein cholesterol (LDL-c), total triglyceride, fasting blood glucose, high-density lipoprotein cholesterol (HDL-c), total cholesterol, serum uric acid serum creatinine, and blood urea nitrogen levels were quantified with automated clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Guangzhou, China. The entire laboratory's measurements were obtained in a manner consistent with a standardization and certification program. The estimated glomerular filtration rate (eGFR) was established with the equation of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), as in those with higher eGFR levels this equation exhibits superior accuracy as compared to the equation of Modification of Diet in Renal Disease (MDRD) [23]. AIP was calculated as follows: \( \log_{10} \left( \frac{\text{triglyceride}}{\text{HDL-c}} \right) \) with each concentration being presented as mmol/L.

**Measurement of baPWV**

BaPWV and the ankle-brachial index (ABI) were measured on the day of blood sample collection using a BP-203RPEIII networked arteriosclerosis detection instrument (Omron Health Care, Kyoto, Japan). Measurements were conducted in a noiseless room with subjects in the supine position following at least 5 minutes of rest. Participants were not permitted to consume tea, alcohol, coffee, or cigarettes for 30 minutes prior to testing. The measurement approaches of baPWV and ABI related to this study have been described previously [24]. Four cuffs were wrapped around ankles and bilateral brachia followed by their connection to an oscillometric pressure sensor and plethysmographic sensor. The ABI was measured by dividing ankle SBP divided with the brachial SBP. Recording the pressure waveforms was carried out with semiconductor pressure sensors for assessing the transmission time between the initial rises in both the tibial and brachial arteries waves. The estimation of the distance between baPWV sampling points was based on height. The formula \( \frac{(La-Lb)}{Tba} \) was used for calculating baPWV. Where La represents the distance between the brachium and the heart, and Tba represents the time interval between the ankle and brachial waveforms. An identical approach was used to measure baPWV for all patients, Right and left baPWV values were averaged for analytical purposes.

**Statistical Analysis**

Continuous data has been presented as means ± standard deviations when normally distributed, or as medians (quartiles) when it is not distributed normally. Categorical variables were given as frequencies or
percentages. These three data types were compared using one-way ANOVAs, Kruskal Wallis H tests, or chi-squared tests, respectively. The relationship between AIP and baPWV was assessed using univariate and multivariate linear regression models. Covariates were adjusted for when, if added to the model, they altered the matched odds ratio by at least 10% [25]. To detect non-linear associations, a generalized additive model (GAM) was also applied. When AIP/baPWV ratio was indicated in a smoothed curve, the inflection point was assessed by considering the recursive approach with a maximum likelihood model. Subgroup analyses were conducted with a stratified multivariate regression approach, and interaction analyses were presented in tabulated form. A likelihood-ratio test was used to assess subgroup interactions.

EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, MA, USA) and R (http://www.R-project.org, The R Foundation) were applied for all statistical analyses. A two-sided P < 0.05 was the significance threshold.

Results

Baseline participant characteristics

In total, 4744 hypertensive patients were enrolled in this study (Figure 1), including 2366 men (49.9%) and 2378 women (50.1%) between the ages of 29 and 93 (mean: 64.50 ± 9.40 years). The mean baseline AIP was -0.00 ± 0.28. Mean baPWV was 18.09 ± 3.88 m/s. Participant baseline characteristics are shown in Table 1. With respect to AIP quartiles, relative to patients with the highest AIP values (Q4) exhibited significantly higher BMI, waist circumference, heart rate, DBP, fasting blood glucose, total triglyceride, and serum uric acid levels compared with all other patients (Q1-Q3), whereas their age and HDL-c levels were significantly lower.

The association between AIP and baPWV

We utilized a multivariate linear regression model for assessing the association between AIP and baPWV (Figure 2). As described in Table 2, in a minimally adjusted model rectified for patient age and sex, AIP was found positively correlated with baPWV (β = 1.07, 95% CI: 0.71 to 1.43, P < 0.001). After adjusting for age, sex, BMI, waist circumference, heart rate, SBP, DBP, fasting blood glucose, total cholesterol, LDL-c, eGFR, serum uric acid, homocysteine levels, self-reported diabetes, coronary artery disease, stroke, current smoking, current drinking, labor intensity, antihypertensive drugs, hypoglycemic drugs, and antiplatelet drugs (multivariate model Ⅰ), AIP remained positively correlated with baPWV (β = 1.34, 95% CI: 0.96 to 1.72, P < 0.001). We additionally treated AIP as a categorical variable, separating patients based upon AIP quartiles, and again observed this same correlation (P for trend < 0.001).

Subgroup analysis results

Stratified and interaction analyses were next conducted for multivariate model Ⅱ (Table 3). The results of testing for interactions were potentially important only for BMI (≥24kg / m² vs. <24kg / m²; P for
interaction = 0.031), whereas these interactions did not display useful results for age (< 60 vs. ≥ 60 years; P for interaction = 0.845), sex (male vs. female; P for interaction = 0.108), SBP (<140, 140-159, ≥160 mmHg; P for interaction = 0.995), DBP (<90, 90-99, ≥100 mmHg; P for interaction = 0.740), eGFR (≥ 60 vs. < 60 ml/min/1.73m2; P for interaction = 0.646), homocysteine levels (≥ 15 vs. < 15 umol/l; P for interaction = 0.802), self-reported diabetes (no vs. yes; P for interaction = 0.949), coronary artery disease (no vs. yes; P for interaction = 0.106), stroke no vs. yes; P for interaction = 0.616), antihypertensive drugs (no vs. yes; P for interaction = 0.087), current smoking (no vs. yes; P for interaction = 0.205), current drinking (no vs. yes; P for interaction = 0.739), or labor intensity (low, middle, high; P for interaction = 0.243). We found that there was a stronger correlation between AIP and baPWV in individuals with a BMI <24 kg/m² (β = 1.72, 95% CI: 1.17 to 2.28).

Discussion

In individuals suffering from hypertension, arterial stiffness appears to be a reliable prognosticator of subclinical vascular disorders and cardiovascular mortalities [26]. Similarly, the increased stiffness is also indicative of asymptomatic target organ damage in these patients [27].

Arterial stiffening is among the primary causes of increased pulse pressure, and is thus a key driver of a range of cardiovascular conditions including atherosclerosis small vessel disease, aneurysm, and left ventricular hypertrophy and failure, thereby contributing to the incidence of myocardial infarction, stroke, and kidney failure [28]. Several studies to date have assessed the relationship between specific serum lipid parameters and arterial stiffness, with multiple prior studies having found elevated triglyceride levels and/or decreased HDL-c levels to be associated with an increase in such stiffness [29–33]. However, some studies showed inconsistent results. Dabelea et al. failed to detect any significant link between triglyceride levels and arterial stiffness (as measured by PWV) in their study of 298 American adolescents with type 1 diabetes [34]. In a separate study of 537 Korean subjects, Kim et al. found triglyceride levels to be correlated with increased arterial stiffness (as measured by baPWV) in both males and females, whereas baPWV was not correlated with HDL-c levels in any analyzed patients [35]. Wei-Chen Shen et al. identified a negative correlation between cfPWV and HDL-c in women over the age of 50 in Taiwan [36]. Therefore, it is limited only to explore the relationship between simple lipid parameters (HDL-c, triglyceride) levels and arterial stiffness.

Based on these results, the AIP (log_{10}[triglyceride/ HDL-c]) has recently been proposed as a superior index that better accounts for the interactions between different lipid fractions, identifying lipid changes in a highly sensitive manner[37]. Relative to more traditional single lipid parameters, AIP exhibits a normal distribution and is thus better suited for the mathematical modeling of key cardiovascular variables [38, 39]. We pay attention to clarify the association between AIP and arterial stiffness using baPWV in the present study. In this large-scale cross-sectional study, we found that AIP was positively correlated with baPWV in hypertensive patients in China after controlling for all potential confounding variables. Si et al. found AIP to be correlated with arterial stiffness in a population of 380 hypertensive Chinese individuals [20]. In line with their results, we detected a positive linear correlation between AIP and baPWV in
hypertensive patients from China. These findings were also in line with data from a prior analysis of 615 normotensive and untreated hypertensive individuals in Finland that found AIP to be associated with cpPWV [19].

The present study has several strengths that warrant discussion. For one, this study was a large-scale analysis of 4744 participants, thus serving as a representative overview of hypertensive Chinese individuals in the real-world. Second, we utilized strict statistical adjustment approaches to minimize the impact of any potential confounding variables on our results, confirming the positive correlation between AIP and arterial stiffness. The use of two indices (triglyceride and HDL-c levels) to yield a single composite index (AIP) offers an effective approach to overcoming inconsistencies in the assessment of different lipid components while simplifying associated predictive analyses. Our data suggest that AIP values can offer information regarding patient arterial stiffness, indicating that this index can be evaluated to diagnose and monitor arterial stiffness in individuals suffering from essential hypertension.

Although the potential mechanisms regarding the relationship of the AIP with arterial stiffness are not entirely clear, it may explain why AIP is positively correlated with arterial stiffness. Arterial stiffening is a complex process associated with vascular damage that occurs due to structural changes in the elastic medial layer of the arteries, including overproduction of collagen, arterial wall thickening, and elastin degradation, all of which may be linked to the onset and progression of arteriosclerosis [40, 41]. The robust value of AIP in the assessment of cardiovascular disease risk is likely linked to its positive relationship with cholesterol esterification rates, lipoprotein particle size, and remnant lipoproteinaemia [42]. AIP reflects the distribution of sdLDL [43, 44], and sdLDL levels are closely linked to oxidative stress and inflammation [45]. Many studies have confirmed oxidative stress and inflammation to contribute to arterial stiffness via aggravating endothelial dysfunction [46], promoting the upregulation of elastin-degrading enzymes [47], driving smooth muscle cell shifts from contractile to synthetic phenotypes [48], and enhancing fibroblast-derived extracellular matrix metallopeptidase expression [49].

In subgroup analyses, we included age, sex, BMI, SBP, DBP, eGFR, homocysteine levels, self-reported diabetes, coronary artery disease, current smoking, stroke, antihypertensive drug use, and labor intensity as potential variables to stratify patients in the present study, but we only ultimately identified a relationship between BMI and the association between baPWV and AIP. We found that for individuals with a BMI < 24 kg/m², AIP and baPWV were stronger correlated with one another. That similar results were not reported by previous studies. Xiao-wei Zhu et al. reported that a higher AIP level was positively associated with obesity in 6465 Chinese participants [50]. Besides, research by Gernot Pichler et al. showed that obesity blunts the increment of cfPWV in women, and patients with BMI levels beyond 25 kg/m² have lower cfPWV compared to normal-weight patients in a cohort of normotensive and hypertensive patients [51]. Hui Yang et al. also reported BMI was negatively and independently associated with baPWV in an elderly Chinese population [52]. The aforementioned findings might be used for explaining the association between AIP and baPWV weakened in overweight individuals. At present, we are unable to well explain the correlation between these two variables stronger with a BMI < 24 kg/m².
and as such further research will be required to understand the impact of overweight on vascular stiffness and how other risk factors shape this relationship.

This study has several limitations that must be considered. For one, this was a study of exclusively Chinese patients with essential hypertension, and may thus not be relevant to other populations. Second, this was a cross-sectional analysis, and we were thus unable to draw any definitive conclusions with respect to the existence of any potential causal relationship between AIP and baPWV. Third, we did not look into the different types of lipid components that may have different effects on arterial stiffness. and as such, further study is required to fully discover the potential association between AIP and baPWV.

**Conclusion**

In summary, we found that AIP was positively correlated with arterial stiffness in Chinese essential hypertension patients, and this relationship was a stronger correlation in those with a BMI < 24 kg/m². These results indicate that AIP may represent a valuable surrogate predictor of arterial stiffness in Chinese hypertensive patients.

**Abbreviations**

AIP, the atherogenic index of plasma; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; baPWV, brachial-ankle pulse wave velocity; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; β, beta coefficient; CI, confidence interval; Ref, reference

**Declarations**

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**Authors' contributions**

FH and RHY participated in literature searches, data analysis, and data interpretation. FH wrote the manuscript. RHY extracted and collected data. MYL, ZGZ, WZ, LLH, LJZ, YRX, HL, XH, and TW conceived of the study and participated in its design and coordination. HHB and XSC participated in the study design and provided critical revisions. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study got approval from the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, and was also consistent with the Declaration of Helsinki. Patients participating in this study provided their written informed consent.

Consent for publication

Not applicable.

Competing Interests

The authors have no conflict of interest to declare.

Clinical trial registration

ChiCTR1800017274.

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**Tables**

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.