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Research Article

# Plasma Cathepsin L Level is Positively Associated with Arterial Stiffness in Geriatric Patients

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**ABSTRACT**

**Background:** Cathepsin L (Cat L) is involved in the regulation of vascular aging processes. The aim of this study was to evaluate the relationship between plasma Cat L level and arterial stiffness marker through brachial-ankle pulse wave velocity (baPWV) in geriatric patients.

**Methods:** Cross-sectional study with 502 people were selected from a population of 2250 people aged over 65 years old, from three different basic health zones of Shanghai. Blood samples were collected, and the baPWV was measured with the SphygmoCor system. The geriatric patients with baPWV values >20 m/s were defined as the high arterial stiffness group.

**Results:** In total, 248 (49.4%) of the 502 geriatric patients in this study were in the high arterial stiffness group. The high arterial stiffness group were older ($p$ = 0.006) and had higher prevalence of hypertension ($p$ = 0.020), coronary heart disease (CHD) ($p$ = 0.037), higher systolic blood pressure (SBP) ($p$ = 0.018), pulse pressure ($p$ = 0.017), plasma Cat L ($p$ = 0.002) and logarithmically transformed C-reactive protein ($p$ = 0.023) levels than those in the low arterial stiffness group. Multivariable forward stepwise regression analysis showed that Cat L ($\beta$ = 0.418, $p$ = 0.011) and hypertension ($\beta$ = 0.217, $p$ = 0.029) were associated with baPWV values in geriatric patients. Moreover, an increased plasma Cat L level (odds ratio (OR): 1.048; 95% confidence interval (CI): 1.043–1.169; $p$ = 0.018) was an independent factor for arterial stiffness among the geriatric patients.

**Conclusion:** In this study, plasma Cat L level was positively correlated with arterial stiffness in geriatric patients.



## 1. INTRODUCTION

Advanced aging prompted vascular aging. As the consequence of vascular aging, arterial stiffness constitutes a potential risk factor for increased cardiovascular mortality in the elderly patients. Its role in the development of Cardiovascular Diseases (CVD) has been more emphatically studied in the past years [1]. Indirect ways to analyze arterial stiffness have been widely studied, Pulse Wave Velocity (PWV) is considered gold standard to evaluate arterial stiffness and is an independent marker of the presence of atherosclerotic cardiovascular diseases. Brachial-ankle PWV (baPWV), an index combining elastic and muscular peripheral arterial stiffness, is a conventional and noninvasive screening method to identify patients at high risk of cardiovascular disease [2,3].

Cysteine protease cathepsins, such as cathepsin L (Cat L), cathepsin K (Cat K), cathepsin S (Cat S), and cathepsin V (Cat V)—are potent elastases and collagenases, play essential roles in the pathogenesis of atherosclerosis in humans and animals [4,5]. In recent decades Cat L has proven to be one of the most valuable gene of aging research [6]. Previous research found that polymorphism in the human Cat L promoter was associated with hypertension [7]. The content and activity of plasma Cat L were increased with age in healthy people [8,9]. Moreover, the plasma Cat L level was correlated with mortality in older adults [10]. We hypothesized that Cat L was associated with arterial stiffness in human. This current study was to determine the relationship between plasma Cat L levels and arterial stiffness measured by baPWV among geriatric patients.

## 2. MATERIALS AND METHODS

### 2.1. Participants and Anthropometric Measurements

The present analysis was an on-going observational multiple-center cross-sectional study recruiting elderly subjects (≥65 years old) in the Shanghai (registry number: ChiCTR-ROC-17013247). Individuals were excluded if they were with rheumatic heart disease, valve heart disease, dilated cardiomyopathy, renal failure, stroke (within 3 months), acute and chronic infections, autoimmune disease and tumor. Between June and October 2018, 502 elderly volunteers aged 65 years or older in Southern Shanghai were enrolled into this study. The present study was approved by the ethics committee of Shanghai Jiao Tong University Affiliated

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Sixth People's Hospital (Shanghai, China). We gave each participant informed consent to the procedure and preserved their anonymity.

In this cross-sectional study, standard structured questionnaire was carried out to obtain the medical and family history including history of hypertension, diabetes, heart disease, drug use, etc. Clinical examination included height, weight, and Body Mass Index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Furthermore, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) was measured in the morning using standard mercury sphygmomanometers. Blood pressure were taken three times at 5-min intervals and were averaged for analysis. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, or the diagnosis of hypertension was documented in a medical record. The diagnosis of stable Coronary Heart Disease (CHD) was based on the clinical history of chest distress/pain, electrocardiogram indicating myocardial ischemia and CT coronary angiography indicating coronary artery occlusion. Type 2 diabetes mellitus was considered if fasting plasma glucose (FBG) ≥126 mg/dL or random plasma glucose ≥198 mg/dL or using diabetes medication. A person was regarded as dyslipidemia if total cholesterol (TC) >200 mg/dL, or low-density lipoprotein-cholesterol (LDL-C) >120 mg/dL, or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women, or triglycerides (TG) >150 mg/dL [11,12].

## 2.2. Biochemical Assessment

Venous blood samples from participants were collected after 8 h of fasting. Each fasting blood sample was immediately centrifuged at 3000 g for 10 min. FBG, TC, TG, HDL-C, LDL-C, creatinine and C-Reactive Protein (CRP) were measured using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland).

## 2.3. Enzyme-linked Immunosorbent Assay

Plasma levels of human Cat L, Cat V, Cat K and Cat S were measured by Enzyme-linked Immunosorbent Assay (ELISA) according to a protocol provided by the manufacturer (Bender Med System, Burlingame, CA, USA). Briefly, 100 µl of diluted human plasma (2:1) samples and 50 µl of biotin-conjugated antibodies were added to 96-well ELISA plates coated with antibody overnight, followed by overnight incubation. A standard curve was created from each plate as recommended using o-phenylenediamine dihydrochloride (OPD) (Sigma, Saint Louis, USA), and a representative of three independent measurements was presented [8,13].

## 2.4. Brachial-Ankle Pulse Wave Velocity Measurements

Brachial-Ankle PWV was measured by Oscillometry-based device (BP-203RPE III; Omron Colin Co., Ltd., Tokyo, Japan). Briefly, each subject was laid in the supine position with PWV cuffs wrapped around both ankles and upper arms. The pulse waveforms were recorded by trained research staff after resting for at least 5 min, and the highest baPWV was recorded for further analysis [3].

## 2.5. Statistical Analysis

Data were tested with the Kolmogorov–Smirnov test for normal distribution. CRP showed skewed non-normally distributions, and therefore were recalculated by logarithm transformation to base 10. All data were presented as means ± standard deviations. The comparison between groups was performed with unpaired student's *t*-test for continuous variables and Chi-square test for categorical variables. The association between clinical variables and baPWV values was evaluated by univariable linear regression analysis and multivariate logistic regression analysis (adopted factors: hypertension, CHD, pulse pressure, age, CRP and Cat L). The results were analyzed using Statistical Product and Service Solutions version 19.0 software (SPSS Inc., Chicago, IL, USA) and $p < 0.05$ was considered statistically significant.

# 3. RESULTS

Until October 2018, 502 subjects who were over 65 years old including 270 (53.8%) men and 232 women were recruited in this study (Table 1). The average age of the sample group was 77.65 ± 5.34 years. According to the value of baPWV, we divided the geriatric patients into low arterial stiffness (baPWV <20 m/s, $n = 254$) group and high arterial stiffness (baPWV >20 m/s, $n = 248$) group. Compared to participants with low arterial stiffness, participants with high arterial stiffness were older ($p = 0.006$) and had higher level of Cat L ($p = 0.002$), SBP ($p = 0.018$), pulse pressure ($p = 0.017$) and Log-CRP level ($p = 0.023$).

Comorbidity and the use of antihypertensives and anti-lipid drugs were presented in Table 2. The medical histories of the geriatric patients included diabetes (33.5%, $n = 168$), dyslipidemia (32.4%, $n = 163$), CHD (27.5%, $n = 138$) and hypertension (45.4%, $n = 228$). The medications prescribed to the geriatric patients included Angiotensin Receptor Blocker (ARB; 29.6%, $n = 149$), Angiotensin Converting Enzyme Inhibitor (ACEI; 13.5%, $n = 68$), Calcium Channel Blockers (CCB; 41.4%, $n = 208$), $\beta$-blocker (31.3%, $n = 157$), aspirin (22.5%, $n = 113$) and statins (14.3%, $n = 72$). Participants in high arterial stiffness group had a higher prevalence of CHD ($p = 0.037$) and hypertension ($p = 0.020$). There were not significant differences in subgroup analysis for gender, medical use of aspirin, $\beta$-blockers, ACEI, statins, ARB or CCB.

The correlation analysis of clinical variables and arterial stiffness in geriatric patients was presented in Table 3. Univariate linear regression analyses revealed that age ($r = 0.247$; $p = 0.028$), plasma Cat L level ($r = 0.275$; $p = 0.016$), SBP ($r = 0.264$; $p = 0.02$), pulse pressure ($r = 0.270$; $p = 0.018$) and Log-CRP ($r = 0.223$; $p = 0.039$) were positively correlated with baPWV value among the geriatric patients. The multivariate, forward stepwise regression analysis shows that Cat L ($\beta = 0.418$, adjusted $R^2$ change = 0.154, $p = 0.011$) and hypertension ($\beta = 0.217$, adjusted $R^2$ change = 0.092, $p = 0.029$) were independent factors of the baPWV value in the elderly patients (Table 4).

Adjustment of the factors significantly associated with arterial stiffness (adopted factors: CHD, hypertension, pulse pressure, age, Log-CRP and Cat L) in multivariate logistic regression analysis showed that elevated plasma Cat L level [odds ratio (OR): 1.048; 95% confidence interval (CI): 1.043–1.169; $p = 0.018$), age (OR: 1.054; 95% CI: 1.011–1.039; $p = 0.021$), and pulse pressure

**Table 1** | Clinical variables of 502 geriatric patients with low or high arterial stiffness

| Characteristics | Total ($n$ = 502) | LAF ($n$ = 254) | HAF ($n$ = 248) | $p$-value |
|---|---|---|---|---|
| Age (years) | 77.65 ± 5.34 | 74.27 ± 5.27 | 81.06 ± 5.06 | 0.006* |
| Body mass index (kg/m²) | 23.78 ± 3.53 | 24.32 ± 3.94 | 23.22 ± 2.98 | 0.052 |
| SBP (mmHg) | 140.19 ± 17.12 | 132.64 ± 18.13 | 147.74 ± 16.15 | 0.018* |
| DBP (mmHg) | 73.75 ± 7.48 | 71.95 ± 7.68 | 74.85 ± 7.38 | 0.058 |
| Pulse pressure (mmHg) | 67.64 ± 9.64 | 61.69 ± 11.45 | 72.89 ± 9.73 | 0.017* |
| Glucose (mg/dL) | 100.8 ± 26.64 | 97.74 ± 23.04 | 103.86 ± 29.88 | 0.139 |
| Total cholesterol (mg/dL) | 156.57 ± 37.90 | 163.61 ± 43.50 | 149.46 ± 30.0 | 0.056 |
| Triglycerides (mg/dL) | 108.62 ± 64.64 | 113.60 ± 70.84 | 102.45 ± 57.55 | 0.078 |
| Creatinine (mg/dL) | 1.01 ± 0.35 | 1.00 ± 0.35 | 1.02 ± 0.36 | 0.947 |
| Log C-reactive protein (mg/dL) | 0.46 ± 0.53 | 0.40 ± 0.47 | 0.52 ± 0.57 | 0.023* |
| Cathepsin S (ng/mL) | 3.41 ± 0.72 | 3.25 ± 0.81 | 3.56 ± 0.53 | 0.142 |
| Cathepsin V (ng/mL) | 0.91 ± 0.24 | 0.90 ± 0.36 | 0.92 ± 0.18 | 0.236 |
| Cathepsin L (pg/mL) | 187.20 ± 44.21 | 160.10 ± 42.36 | 214.4 ± 46.06 | 0.002* |
| Cathepsin K (pmol/L) | 107.4 ± 53.7 | 106.8 ± 51.9 | 109.5 ± 51.5 | 0.426 |
| baPWV (m/s) | 20.85 ± 5.49 | 16.79 ± 2.16 | 25.00 ± 4.69 | <0.001* |

*$p$ < 0.05 is considered statistically significant. Values were given as means ± SD and tested by Student's $t$-test; Data of C-reactive protein showed skewed distribution and therefore was log-transformed before analysis. LAF, low arterial stiffness; HAF, high arterial stiffness; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 2** | Distribution of 502 geriatric patients with low or high arterial stiffness in subgroup analysis

| Characteristics | LAF (%) | HAF (%) | $p$-value |
|---|---|---|---|
| Gender | | | |
| Female | 118 (46.3) | 114 (46.1) | 0.987 |
| Male | 136 (53.7) | 134 (53.9) | |
| Diabetes | | | |
| No | 178 (70.2) | 156 (62.9) | 0.068 |
| Yes | 76 (29.8) | 92 (37.1) | |
| Hypertension | | | |
| No | 177 (69.7) | 97 (39.3) | 0.020* |
| Yes | 77 (30.3) | 151 (60.7) | |
| Coronary heart disease | | | |
| No | 197 (77.6) | 167 (67.3) | 0.037* |
| Yes | 57 (22.4) | 81 (32.7) | |
| Dyslipidemia | | | |
| No | 183 (72.1) | 156 (62.9) | 0.159 |
| Yes | 71 (27.9) | 92 (37.1) | |
| Aspirin use | | | |
| No | 200 (78.7) | 189 (76.2) | 0.068 |
| Yes | 54 (21.3) | 59 (23.8) | |
| ARB use | | | |
| No | 203 (80.0) | 150 (60.6) | 0.108 |
| Yes | 51 (20.0) | 98 (39.4) | |
| $\beta$-Blocker use | | | |
| No | 204 (80.1) | 142 (57.1) | 0.060 |
| Yes | 51 (19.9) | 106 (42.9) | |
| CCB use | | | |
| No | 161 (63.3) | 133 (53.6) | 0.451 |
| Yes | 93 (36.7) | 115 (46.4) | |
| Statin use | | | |
| No | 227 (89.4) | 203 (82.0) | 0.390 |
| Yes | 27 (10.6) | 45 (18.0) | |
| ACEI use | | | |
| No | 230 (90.5) | 204 (82.1) | 0.381 |
| Yes | 24 (9.5) | 44 (17.9) | |

*$p$ < 0.05 is considered statistically significant. Data are expressed as $n$ (%) of old adults with low or high arterial stiffness and analysis was done using the Chi-square test. LAF, low arterial stiffness; HAF, high arterial stiffness; ARB, Angiotensin receptor blockers; CCB, Calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitor.

**Table 3** | Correlation of clinical variables and brachial-ankle pulse wave velocity in univariate linear regression analysis among the 502 geriatric patients

| Variables | $r$ | $p$-value |
|---|---|---|
| Age (years) | 0.247 | 0.028* |
| Body mass index (kg/m²) | 0.062 | 0.433 |
| Systolic blood pressure (mmHg) | 0.264 | 0.020* |
| Diastolic blood pressure (mmHg) | 0.062 | 0.433 |
| Pulse pressure (mmHg) | 0.270 | 0.018* |
| Total cholesterol (mg/dL) | −0.088 | 0.259 |
| Triglycerides (mg/dL) | −0.004 | 0.961 |
| Glucose (mg/dL) | 0.868 | 0.606 |
| Log-C-reactive protein (mg/dL) | 0.223 | 0.039* |
| Cathepsin S (ng/mL) | 0.178 | 0.151 |
| Cathepsin V (ng/mL) | 0.019 | 0.866 |
| Cathepsin K (pmol/L) | −0.168 | 0.143 |
| Cathepsin L (pg/mL) | 0.275 | 0.016* |
| Creatinine (mg/dL) | 0.103 | 0.185 |

*$p$ < 0.05 is considered statistically significant. Data of C-reactive protein showed skewed distribution and therefore was log-transformed before analysis.

**Table 4** | Multivariate forward stepwise regression analysis of the factors correlated with brachial-ankle pulse wave velocity among 502 geriatric patients

| Items | $\beta$ | Adjusted $R^2$ | Adjusted $R^2$ change | $p$-value |
|---|---|---|---|---|
| Cathepsin L (pg/mL) | 0.418 | 0.154 | 0.154 | 0.011* |
| Hypertension | 0.217 | 0.319 | 0.092 | 0.029* |

*$p$ < 0.05 was considered statistically significant. Analysis was done using multivariate logistic regression analysis (adopted factors: hypertension, age, systolic blood pressure, log C-reactive protein, coronary heart disease, pulse pressure and cathepsin L).

(OR: 1.067; 95% CI: 1.023–1.229; $p$ = 0.038) were independent factors of arterial stiffness among the elderly patients (Table 5).

## 4. DISCUSSION

This study reported that the plasma Cat L level was positively associated with arterial stiffness and was an independent factor of the

**Table 5** | Multivariate logistic regression analysis of the factors correlated with brachial-ankle pulse wave velocity among 502 geriatric patients

| Variables | OR (95% CI) | *p*-value |
|---|---|---|
| Age (years) (each increase of 1 year) | 1.054 (1.011–1.039) | 0.021* |
| Pulse pressure (mmHg) (each increase of 1 mmHg) | 1.067 (1.023–1.229) | 0.038* |
| Cathepsin L (pg/mL) (each increase of 1 pg/mL) | 1.048 (1.043–1.169) | 0.018* |

*$p < 0.05$ was considered statistically significant. Analysis was done using multivariate logistic regression analysis (adopted factors: hypertension, age, systolic blood pressure, log C-reactive protein, coronary heart disease, pulse pressure and cathepsin L). OR, odds ratio; CI, confidence interval.

baPWV value in geriatric patients. Arterial stiffness is recognized as a surrogate end point for CVD and characterized by a thickening and loss of elasticity of the arterial wall. The increased macrophage apoptosis and matrix degradation by lysosomal enzymes such as cathepsins may play important roles in atheroma [14]. Cathepsins was one of major protease systems expressed in the arteries [15]. Vascular cells such as vascular endothelium, and smooth muscles are important sources of Cat L [16]. Cat L promotes vascular intimal hyperplasia after arterial injury [17]. Hypertension, the most potent risk factor for CVD, can drive pathologic remodeling of the macro-and microcirculation. Previous research showed that Cat L catalyzes the formation of peptides that influence blood pressure and was involved in the autophagy of hypertensive and atherosclerosis [18–20]. Moreover, Cat L is shear-sensitive and upregulated during vascular remodeling [21]. Under the influence of inflammation, the vascular wall may secrete Cat L into the circulation due to oscillatory vortex flows in multiple branches, narrows during cardiac systolic and diastolic process and result in elevated plasma Cat L. In previous research, Cat L have been investigated as biomarkers for CVD [10,14,16,22]. The results of the present study also showed that plasma Cat L level was positively associated with arterial stiffness and was an independent factor for the baPWV value in geriatric patients.

Cardiovascular disease is the leading cause of death in many developed countries. Large elastic artery stiffening is an independent predictor of future CVD diagnosis and likely are responsible for the development of CVD in older adults [23,24]. Arterial hypertension is a common disease with great harm. The risk of hypertension after 55 years old was 90% [25]. Advanced age promotes greater elastic arteriosclerosis, leading to a gradual increase in pulse pressure [26]. Our results noted higher prevalence of hypertension, CHD, elevated SBP and elevated pulse pressure in the high arterial stiffness group. Moreover, age and pulse pressure were an independent factor for the baPWV value after multivariate adjustment.

Inflammation is a major feature in the initiation and progression of atherosclerosis and subsequent CVD [27]. High sensitivity CRP is well-validated, inexpensive, and widely available inflammatory marker [28]. Some researches had showed that CRP is associated with arterial stiffness in a cohort of African-American and white women transitioning through menopause and even in healthy individuals [29,30]. The current study also revealed a correlation between CRP levels and baPWV value in a univariate linear regression analysis. But this correlation did not remain after multivariate adjustment.

There are a few limitations in our study. First, since our study participants were elderly patients from a few medical centers at Southern Shanghai, and further assessment is needed to determine whether the results are applicable to other populations. Second, the study was an across-sectional design, which may affect the statistical significance. Further long-term prospective studies are needed to confirm the relationship between arterial stiffness and Cat L level.

In conclusion, our results demonstrated that higher Cat L plasma level was associated with arterial stiffness in geriatric patients. Moreover, age and pulse pressure were also positively associated with the baPWV value in these geriatric patients.

## CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

## AUTHOR'S CONTRIBUTION

GXF did study conceptualization and wrote (review and editing) the manuscript. CCX and FFP did the data curation. CCX, FFP and JX did the formal analysis and writing (original draft). Project administration and supervision were carried out by TJH and YZ.

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