

Positive correlation of the serum angiopoietin-like protein 3 levels with the aortic augmentation index in patients with coronary artery disease

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Purpose: Angiopoietin-like protein 3 (ANGPTL3) plays an important role in lipid metabolism and angiogenesis and is elevated in familial hypercholesterolemia, metabolic syndrome, and insulin resistance. This study aims to evaluate the relationship between the fasting serum ANGPTL3 levels and the aortic augmentation index (Aix) in patients with coronary artery disease (CAD).

Materials and methods: Fasting blood samples were obtained from 100 patients with CAD. The Aix was measured using a validated tonometry system (SphygmoCor). The serum ANGPTL3 levels were assessed using a commercial enzyme-linked immunosorbent assay kit.

Results: The aortic Aix values were higher in female patients with CAD ($P=0.003$) than those in male patients with CAD. The univariate linear analysis of the aortic Aix values reveals that the height ($r=-0.363$; $P<0.001$) and body weight ($r=-0.350$; $P<0.001$) were negatively correlated, whereas the age ($r=0.202$; $P=0.044$) and logarithmically transformed ANGPTL3 ($\log\text{-ANGPTL3}$, $r=0.357$; $P<0.001$) were positively correlated with the aortic Aix values in patients with CAD. The multivariate forward stepwise linear regression analysis of the factors significantly associated with the aortic Aix revealed that the height ($\beta=-0.269$; adjusted R^2 change=0.123; $P=0.007$) and serum $\log\text{-ANGPTL3}$ level ($\beta=0.259$; adjusted R^2 change=0.051; $P=0.010$) were independent predictors of the aortic Aix values in patients with CAD.

Conclusion: The fasting serum ANGPTL3 level positively correlated with the aortic Aix values among patients with CAD.

Keywords: ANGPTL3, ischemic heart disease, arterial stiffness, height, aortic augmentation index, SphygmoCor

Introduction

Angiopoietin-like proteins (ANGPTL) are a family of proteins that have similar structures as angiopoietin proteins that are reportedly involved in the regulation of lipid metabolism.¹ Angiopoietin-like protein 3 (ANGPTL3) is a secretory protein regulating plasma lipid levels by affecting lipoprotein lipase- and endothelial lipase-mediated hydrolysis of phospholipids and triglycerides (TG).² In humans, participants with heterozygous loss-of-function variants in ANGPTL3 had significantly lower serum levels of TG, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) than participants without these variants.³

Arterial stiffness results from a degenerative process affecting mainly the extracellular matrix of elastic arteries under the effect of aging and atherosclerosis, changes in the elastic elements of the arterial wall, endothelial dysfunction, and inflammation.⁴ Moreover, arterial stiffness and dyslipidemia are crucial determinants of cardiovascular

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risk.⁵ The aortic augmentation index (AIx) is a measure of pulse wave reflection that calculates the central pulse pressure accounted for by the reflected pulse wave and is often referred to as a marker of arterial stiffness.⁶ Some studies have suggested that the aortic AIx is significantly related to the degree of coronary artery disease (CAD).^{7,8} Therefore, this study aimed to examine the aortic stiffness by assessing the aortic AIx and serum ANGPTL3 in patients with CAD.

Materials and methods

Patients

Between March and December 2012, 115 patients with CAD (CAD was defined as >50% stenosis in any segment by coronary angiography by medical record) in a medical center in Hualien, eastern Taiwan were enrolled; 15 participants were excluded because of acute infection (n=2); pulmonary edema (n=1); use of calcium, active vitamin D metabolites, bisphosphonates, teriparatide, or estrogens medication (n=5); and refusal to provide informed consent (n=7). Finally, a total of 100 CAD patients (74 males and 26 females) were enrolled in this study. The Protection of the Human Subjects Institutional Review Board of Tzu Chi University and Hospital (Hualien, Taiwan) approved this study. Informed written consent was obtained from all patients before their enrollment in this study. Trained staff members measured the blood pressure (BP) of all participants in the morning, using standard mercury sphygmomanometers with appropriate cuff sizes after the participants had been sitting for at least 10 min. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken at the points of appearance and disappearance, respectively. Hypertension was defined as SBP \geq 140 mmHg and/or DBP \geq 90 mmHg or prescription of antihypertensive medication in the past 2 weeks. A person was regarded as diabetic if the fasting plasma glucose was either 126 mg/dL or more or if he/she was using diabetes medication (oral or insulin).⁹

Anthropometric analysis

Patient's weight was measured in light clothing and without shoes to the nearest 0.5 kg, and the height was assessed to the nearest 0.5 cm. The body mass index was calculated as the weight in kilograms divided by the height in meters squared.^{10–12}

Biochemical investigations

After 8–12 h overnight fasting, blood (~5 mL) of all participants was sampled in the morning, of which ~0.5 mL was used to determine hemoglobin and white blood cells count (Sysmex K-1000; Sysmex America, Mundelein, IL, USA); the remainder was immediately centrifuged at

3,000 \times g for 10 min. The serum levels of blood urea nitrogen (BUN), creatinine (Cre), fasting glucose, total cholesterol, TG, HDL-C, LDL-C, total calcium, and phosphorus were measured using an autoanalyzer (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland).^{10–12} The serum ANGPTL3 (R&D Systems, Inc., Minneapolis, MN, USA) and intact parathyroid hormone (iPTH; Diagnostic Systems Laboratories, Webster, TX, USA) concentrations were quantified using commercial enzyme-linked immunosorbent assay.^{11–13} The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

Pulse wave analysis and AIx assessment

The pulse wave analysis and AIx assessment were arranged on the same day after blood sampling and not necessarily in fasting status. Patients were positioned supine and allowed to rest for 10 min before the test was performed. Although the consumption of food, drink, alcohol, or tobacco was not restricted, patients were not allowed to sleep or talk during the testing procedure. The pulse wave analysis by applanation tonometry was performed on the right radial artery and analyzed by the SphygmoCor software (SphygmoCor system; AtCor Medical, Australia), which also calculates a number of major indices including the aortic AIx.^{6,11,12}

Statistical analysis

Normally distributed data were expressed as the mean \pm SD and comparisons between patients were performed using the Student's independent *t*-test (two-tailed). Data not normally distributed were expressed as medians and interquartile ranges. The TG, glucose, BUN, Cre, and ANGPTL3 data sets revealed skewed non-normal distributions and therefore were recalculated by transformation to the logarithm to the base 10; after this transformation, the log-TG, -glucose, -BUN, -Cre, and -ANGPTL3 exhibited a normal distribution. The clinical variables that correlated with the aortic AIx values in patients with CAD were evaluated using the univariate linear regression analysis first. However, the variables that were significantly associated with the aortic AIx in patients with CAD were tested for independence by the multivariate forward stepwise regression analysis (adapted factors: age, sex, height, body weight, and log-ANGPTL3). All data were analyzed using the SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). *P* < 0.05 was considered statistically significant.

Results

The demographic, biochemical, and clinical characteristics of 100 patients with CAD are shown in Tables 1 and 2.

Table 1 Clinical and analytical characteristics of 100 patients with coronary artery disease

Items	Parameter	Values	Parameter	Values
Anthropometric data	Age (years)	65.41±9.05	Height (cm)	160.82±8.35
	Body weight (kg)	68.04±11.79	Body mass index (kg/m ²)	26.21±3.35
	Aortic augmentation index (%)	24.17±9.43	SBP (mmHg)	130.98±16.80
	DBP (mmHg)	72.46±10.31		
Biochemical data	White blood count (×1,000/μL)	6.43±1.64	Hemoglobin (g/dL)	14.25±1.52
	Triglyceride (mg/dL)	119.00 (90.25–162.00)	Total cholesterol (mg/dL)	164.57±35.93
	HDL-C (mg/dL)	44.90±11.79	LDL-C (mg/dL)	95.01±26.27
	Fasting glucose (mg/dL)	111.50 (97.00–145.25)	Creatinine (mg/dL)	1.10 (0.90–1.30)
	Blood urea nitrogen (mg/dL)	16.00 (13.00–19.00)	eGFR (mL/min)	68.36±19.30
	Total calcium (mg/dL)	9.13±0.37	Phosphorus (mg/dL)	3.55±0.52
	iPTH (pg/mL)	52.94±27.79	ANGPTL3 (ng/mL)	246.02 (148.86–307.20)

Note: Values for continuous variables given as mean ± SD and variables not normally distributed given as medians and interquartile range.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; ANGPTL3, angiotensin-like protein 3.

Patients' medical histories included diabetes mellitus (n=47; 47.0%) and hypertension (n=77; 77.0%). The use of drugs included angiotensin-converting enzyme inhibitor (ACEI; n=30; 30.0%), angiotensin-receptor blocker (ARB; n=39; 39.0%), calcium-channel blocker (CCB; n=32; 32.0%),

β blocker (n=57; 57.0%), statins (n=66; 66.0%), and fibrates (n=14; 14.0%). The aortic AIx values in female patients with CAD ($P=0.003$) were higher than in male patients with CAD. No statistically significant difference based on ACEI, ARB, β blocker, CCB, statins, or fibrates use in the aortic AIx values was noted.

Table 3 shows the univariate linear regression analysis of the aortic AIx values for patients with CAD. In participants

Table 2 Clinical characteristics and AIx levels of 100 patients with coronary artery disease

Characteristic	Number	AIx (%)	P-value
Gender			0.003*
Male	74	22.55±8.30	
Female	26	28.77±11.02	
Diabetes			0.204
No	53	23.04±10.44	
Yes	47	25.45±8.06	
Hypertension			0.366
No	23	25.74±10.58	
Yes	77	23.70±9.08	
Angiotensin-converting enzyme inhibitor			0.422
No	70	23.67±9.11	
Yes	30	25.33±10.21	
Angiotensin-receptor blocker			0.595
No	61	24.57±10.38	
Yes	39	23.54±7.81	
β blocker			0.533
No	43	23.49±8.78	
Yes	57	24.68±9.94	
Calcium-channel blocker			0.163
No	68	23.26±9.70	
Yes	32	26.09±8.68	
Statin			0.341
No	34	22.91±11.67	
Yes	66	24.82±8.07	
Fibrate			0.110
No	86	24.78±9.25	
Yes	14	20.43±10.05	

Note: * $P<0.05$ was considered statistically significant after the Student's independent t-test.

Abbreviation: AIx, augmentation index.

Table 3 Correlation of AIx levels and clinical variables by univariate linear regression analysis among 100 patients with coronary artery disease

Variable	r-value	P-value
Age (years)	0.202	0.044*
Height (cm)	-0.363	<0.001*
Body weight (kg)	-0.350	<0.001*
Body mass index (kg/m ²)	-0.181	0.071
Systolic blood pressure (mmHg)	0.157	0.120
Diastolic blood pressure (mmHg)	0.095	0.347
White blood count (×1,000/μL)	0.110	0.275
Hemoglobin (g/dL)	-0.107	0.289
Total cholesterol (mg/dL)	0.036	0.721
Log-TG (mg/dL)	0.046	0.649
HDL-C (mg/dL)	-0.060	0.556
LDL-C (mg/dL)	0.089	0.376
Log-glucose (mg/dL)	0.030	0.768
Log-BUN (mg/dL)	-0.044	0.661
Log-Cre (mg/dL)	-0.126	0.211
eGFR (mL/min)	0.010	0.922
Total calcium (mg/dL)	0.062	0.542
Phosphorus (mg/dL)	-0.041	0.684
Intact parathyroid hormone (pg/mL)	-0.098	0.333
Log-ANGPTL3 (ng/mL)	0.357	<0.001*

Notes: Data of the TG, glucose, BUN, Cre, and ANGPTL3 levels showed skewed distribution and therefore were log-transformed before the analysis. * $P<0.05$ is considered statistically significant in the univariate linear analyses.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ANGPTL3, angiotensin-like protein 3; TG, triglycerides; BUN, blood urea nitrogen; Cre, creatinine.

Table 4 The multivariate stepwise linear regression analysis of the age, gender, height, body weight, and ANGPTL3: correlation to AIX levels among 100 patients with coronary artery disease

Items	β	Adjusted R^2	Adjusted R^2 change	P-value
Height (cm)	-0.269	0.123	0.123	0.007*
Log-ANGPTL3 (ng/mL)	0.259	0.174	0.051	0.010*

Note: * $P < 0.05$ is considered statistically significant in the multivariate stepwise linear regression analysis.

Abbreviations: ANGPTL3, angiopoietin-like protein 3; AIX, augmentation index.

of this study, the height ($r = -0.363$; $P < 0.001$) and body weight ($r = -0.350$; $P < 0.001$) were negatively correlated with the aortic AIX, whereas the age ($r = 0.202$; $P = 0.044$) and logarithmically transformed ANGPTL3 (log-ANGPTL3, $r = 0.357$; $P < 0.001$) were positively correlated with the aortic AIX. The variables that were significantly associated with the aortic AIX values (adapted factors: age, sex, height, body weight, and log-ANGPTL3) were analyzed using the multivariate forward stepwise linear regression analysis, which revealed that the height ($\beta = -0.269$; adjusted R^2 change = 0.123; $P = 0.007$) and serum log-ANGPTL3 level ($\beta = 0.259$; adjusted R^2 change = 0.051; $P = 0.010$) were independent factors that were associated with the aortic AIX in our patients with CAD (Table 4).

Discussion

This study suggests that the age, female sex, and fasting serum ANGPTL3 level positively correlated with the aortic AIX values among patients with CAD. Conversely, the height and body weight were negatively correlated with the aortic AIX values. The height and serum log-ANGPTL3 level were independent factors associated with the aortic AIX values in our patients with CAD after adjustment for the age, sex, and body weight.

Several studies have suggested that the aortic AIX values were inversely correlated with height and were higher in females.^{14–17} Reportedly, arterial wave reflections occur later in taller individuals because the distance from the heart to the reflection point is longer, causing greater time of reflection in taller people.⁷ This assertion could explain the reason why the AIX value was consistently higher in women than that in men.^{14–17} The aortic AIX value is also higher in girls than that in boys at 14 years and is closely associated with the change in the height between 8 and 14 years in adolescents.¹⁸ Reeve et al noted that taller individuals had more favorable central hemodynamics and reduced evidence of CAD compared with those of shorter individuals.¹⁹ The results of our study

revealed that female patients with CAD had higher aortic AIX values, and height is negatively associated with the aortic AIX values in patients with CAD. After the adjustment of other factors, such as gender, the multivariate forward stepwise linear regression analysis showed that the height was negatively associated with the aortic AIX values in patients with CAD.

With aging, the vasculature undergoes structural and functional changes characterized by vascular fibrosis and arterial stiffening.²⁰ The aortic AIX values were significantly and independently associated with the age.^{17,21} Our results also noted that the age is positively associated with the aortic AIX values in patients with CAD. In patients with chronic kidney disease, body weight is inversely associated with the aortic AIX values.²² Furthermore, weight loss was significantly and independently associated with each reduction in the aortic AIX values after a 12-week training program among Japanese elderly persons.²³ However, weight loss induced by energy restriction did not improve the aortic AIX values in a systematic review and meta-analysis of clinical trials involving adult subjects.²⁴ Another study identified that changes in the AIX values were related to changes in the abdominal fat and total body fat percent when adjusted for gender and relevant baseline confounders.²⁵ Although this study noted that body weight is negatively associated with the aortic AIX values in patients with CAD, future research is required to prove this finding.

Hyperlipidemia is associated with reduced nitric oxide bioavailability and endothelial dysfunction, which may lead to the increase in the aortic AIX values and arterial stiffness.²⁶ The aortic AIX value was significantly higher in patients in the hypercholesterolemia group.²⁷ Moreover, patients with hypercholesterolemia have stiffer blood vessels than matched controls, and the hemodynamic change might contribute to the increased risk of cardiovascular disease.⁴ ANGPTL3 regulates the TG metabolism by reversibly inhibiting the lipoprotein lipase activity.¹ ANGPTL3 deficiency causes enhanced activity of lipoprotein lipase in the muscle and adipose tissue and accelerates the clearance of TG-rich lipoproteins. The decreased lipolysis in adipose tissue results in a scarcity of free fatty acid substrates for hepatic de novo synthesis of TG and cholesterol, and, consequently, decreased lipidation of very low-density lipoprotein cholesterol.² In an animal study, ANGPTL3 deficiency and the resulting hypolipidemia were protective against the development of atherosclerosis.² In human studies, ANGPTL3 deficiency is associated with the protection from CAD.^{3,28} Therapeutic antagonism of ANGPTL3 (evinacumab) in

humans caused a dose-dependent placebo-adjusted reduction in fasting TG levels of up to 76% and LDL-C levels of up to 23%.³ In contrast, the aortic AIx value was shown to be significantly correlated with cardiovascular risk.^{29,30} The results of our study further confirmed that the serum ANGPTL3 level was also positively associated with the aortic AIx values in patients with CAD after the adjustment of other confounders.

Limitations

There are limitations of this study that need to be highlighted. First, the sample size is small. Perhaps, larger study groups of patients with CAD could increase the accuracy of results. Second, this study was an observational study; therefore, further longitudinal studies are needed before a cause–effect relationship between the serum ANGPTL3 level and the aortic AIx value can be established in patients with CAD. In addition, the use of medication for hypertension may affect the AIx values. Studies have noted that the use of ACEIs or statins has a beneficial effect on the aortic AIx value, which is independent of BP reduction or LDL-C changes.^{31,32} The results of this study did not demonstrate a correlation between antihypertensive drugs, statins, or fibrates used with the aortic AIx values in patients with CAD. Finally, current smoking³³ and smoking pack years³⁴ may affect aortic AIx values. Further studies are required to elucidate the relationship between aortic AIx values and smoking and serum ANGPTL3 level in CAD patients.

Conclusion

Our study reveals that the fasting serum ANGPTL3 level positively correlated with the aortic AIx values, whereas the height negatively correlated with the aortic AIx values among patients with CAD. Further prospective studies are needed to confirm the mechanisms underlying this association.

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Author contributions

YSF, BGH, and JHW conceived and designed the experiments. CJL and JHW performed the experiments. BGH and CJL analyzed the data. YSF, BGH, and JHW wrote the manuscript. All of the authors reviewed and approved the final version of this paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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