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Coronary Artery Disease

Impact of Apelin-13 on the Development of Coronary Artery Ectasia

Xusen Sun,[1,2] Yufan Zhang,[1,2] Xin Qi[2] and Liping Wei[2]

Background: Coronary artery ectasia (CAE) is the limitation or diffuse expansion of the epicardial coronary artery. In most cases, the pathological basis of CAE is considered to be coronary atherosclerosis. Previous studies have confirmed the association between Apelin and arterial atherosclerosis. Apelin-13 (AP-13) is the main serum Apelin subtype in healthy humans, however the effect of serum AP-13 on CAE has yet to be elucidated. In this research, we analysed the relationship between serum AP-13 levels and CAE.

Methods: One hundred and forty subjects who underwent selective diagnostic coronary angiography were enrolled in this research. We identified and included 40 patients with CAE as the study subjects. Another 50 patients with coronary artery disease (CAD) were randomly selected as the CAD group, and 50 patients without CAD were selected as the normal control group. Serum AP-13 levels were collected for all subjects.

Results: There were no statistically significant differences in baseline data except for gender. After unconditional logistic regression analysis, AP-13 and HDL-c were independent risk factors for CAE (both $p < 0.05$). The serum AP-13 level was significantly lower in the CAE patients than in the CAD patients (1.86 ± 0.59 vs. 2.49 ± 1.19 ng/mL, $p = 0.004$). Serum AP-13 levels were slightly lower in the CAD patients than in the controls (2.49 ± 1.19 vs. 3.12 ± 1.64, $p = 0.079$).

Conclusions: Apelin-13 may have an effect on the development of CAE. Further studies should be performed to elucidate the possible pathogenic role of AP-13 in CAE.

Key Words: Apelin-13 • Atherosclerosis • Coronary artery disease • Coronary artery ectasia

INTRODUCTION

Coronary artery ectasia (CAE) is a rare abnormal kind of non-obstructive coronary artery disease (CAD) in which the lesion adjacent to the normal coronary artery lumen has a diameter that is 1.5 times the normal diameter.[1] The incidence is 1~5%.[2] The clinical manifestations of CAE are diverse and are often similar to the clinical manifestations of CAD,[3] and therefore it is generally considered to be a variant of coronary atherosclerosis.[4] The pathogenesis of coronary dilation may be related to endothelial dysfunction or to the interaction of inflammatory factors.[5,6]

Apelin-angiotensin receptor (APJ) was the first orphan G-white coupling receptor discovered by O'Dowd in 1993.[7] Tatemoto first extracted a new vasoactive peptide, Apelin, from cow stomach secretions in 1998.[8] Apelin is the endogenous ligand of the APJ, and the Apelin/APJ system is widely distributed in peripheral and central regions. Apelin has several subtypes: Apelin-12, Apelin-13, Apelin-17, Apelin-28 and Apelin-36. Apelin-13 (AP-13) has strong biological activity and many functions, and it is the main subtype of Apelin in the heart, brain and hypothalamus. Apelin-13 is involved in the physiological and pathological processes of the cardiovascular system, respiratory system, nervous system, digestive system and endocrine system. When AP-13 binds

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[1]Tianjin Medical University; [2]Department of Cardiology, Tianjin Union Medical Center, Tianjin, China.
Corresponding author: Dr. Liping Wei, Department of Cardiology, Tianjin Union Medical Center, No. 190, Jieyuan Road, Hongqiao District, Tianjin 300121, China. E-mail: sxstjmu@163.com

to the APJ receptor, it can antagonize angiotensin II to contractile blood vessels,[9] thereby forming diastolic blood vessels and lowering blood pressure.[10,11] An epidemiological survey of Chinese coastal populations showed that AP-13 was negatively correlated with systolic blood pressure, diastolic blood pressure and mean arterial pressure.[12] However, the effect of serum AP-13 levels on CAE has yet to be elucidated. Thus, we analysed the relationship between serum AP-13 levels and CAE in this study.

MATERIALS AND METHODS

Subjects

All of the subjects were randomly selected from the population of patients undergoing coronary angiography at the cardiology department of Tianjin Union Medical Center. The subjects were divided into three groups according to the coronary angiography results. The first group was the normal control group (n = 50; 15 males and 35 females; average age 58.06 ± 9.51 years). The second group was the CAD group (n = 50; 29 males and 21 females; average age 62.08 ± 8.29 years). The third group was the CAE group (n = 40; 26 males and 14 females; average age 61.28 ± 8.46 years). The results of coronary angiography and inpatient records were reviewed, and relevant clinical data were collected. The exclusion criteria were: history of acute myocardial infacrtion (AMI), pulmonary embolism, aortic dissection, cardiomyopathy, severe valvular heart disease, symptomatic cardiac insufficiency, history of percutaneous coronary intervention or coronary artery bypass grafting, severely incomplete liver and kidney function, peripheral vascular disease, blood disease, malignant tumour, acute and chronic infection, autoimmune disease, and stroke. Hypertension was defined as a systolic blood pressure above 140 mmHg (1 mmHg = 133 Pa) and/or a diastolic blood pressure above 90 mmHg, or the current use of antihypertensive drugs. Diabetes was defined as a fasting blood glucose above 5.6 mmol/L, or the current use of a hypoglycemic intervention. Hyperlipidemia was defined as a total cholesterol content of more than 200 mg/dL, or a diagnosis of hyperlipidemia and the current use of medications to regulate lipids. The study protocol was approved by the local ethics committee, and all patients signed a written informed consent form. CAD was defined as an arbitrary coronary artery with more than 50% lumen stenosis. CAE was defined as a limited or diffusely expanded coronary artery with a diameter 1.5 times greater than that of the adjacent normal vessels.

Biochemical measurements

Fasting elbow venous blood samples of the patients were collected in a test tube the next morning. After centrifugation of the samples (3000 rpm for 15 min), the supernatant samples were stored at -80 °C in a refrigerator until analysis. Routine blood samples were analyzed using a XE-1200 automated hematology analyzer (Sysmex, Kobe, Japan). Other biochemical measurements (blood lipids, blood uric acid, blood urea nitrogen, serum creatinine, fasting glucose, hypersensitive C-reactive protein and cystatin C, and homocysteine levels) were performed in the clinical laboratory center using a molecular analyzer (Roche Diagnostics, Manheim, Germany). Serum AP-13 level was detected by enzyme-linked immunosorbent assay (Cloud-Clone Corp., US).

Coronary angiography

All angiography evaluations were completed in the interventional therapy room at our hospital using the Seldinger puncture technique in the right radial artery or femoral artery, in which a right 6F Judkins catheter was inserted through left and right coronary artery openings, left coronary artery from the head, right shoulder, right front incline, liver and spider projection, right coronary artery by the left anterior oblique position and head bearing such a projection. The procedures were performed by two or more experienced clinical cardiac interventional physicians. The visual readings and records of the results of the coronary angiography (CAG) patients were analysed in detail.

Statistical analysis

Continuous variables are expressed as the means plus or minus the standard deviation ($\bar{x} \pm s$), and classification variables are expressed as a percentage. The levels of serum AP-13 among the three groups showed a normal distribution, and one-way ANOVA was used to analyze this. Comparisons of data between the other groups were based on single-factor variance analysis of

multiple groups and the statistical methods of multiple groups using the chi-square test. The statistical methods of logistic regression analysis for possible risk factors using dichotomous variables were defined as being statistically significant at $p < 0.05$. All statistical analyses of the data were performed using SPSS 23.0.

RESULTS

Comparisons of general data of the CAE group, CAD group and control group

The CAE group, CAD group and control group were compared, and differences in the groups in age, body mass index, history of hypertension, history of diabetes, smoking history, drinking history, family history of CAD and previous medications were not statistically significant ($p > 0.05$). However, the CAE group and CAD group had a statistically significant difference in gender compared with the control group ($p = 0.002$) (Table 1).

Comparisons of the biochemical indexes of the CAE group, CAD group and control group

After comparing the three groups, indicators including white blood cell count (WBC) and lymphocyte count, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), very low-density lipoprotein cholesterol (VLDL-c), cystatin C, blood uric acid, and creatinine, were not statistically significant ($p > 0.05$). There were significant differences in highdensity lipoprotein cholesterol (HDL-c) and blood glucose levels between the CAE group and control group ($p < 0.05$). There was a significant difference in homocysteine level between the CAD group and control group ($p < 0.001$). In addition, the serum AP-13 level in the CAE group was lower than that in the CAD group and the control group ($p = 0.004$) (Table 2).

Correlation of coronary artery ectasia and analysis of risk factors

Non-conditional logistic regression analysis indicated that AP-13 and HDL-c were risk factors for CAE [AP-13: odds ratio (OR) = 0.316, 95% confidence interval (CI): 0.156~0.640, $p = 0.001$; HDL-c: OR = 0.001, 95% CI: 0.000~0.045, $p < 0.001$] (Table 3).

DISCUSSION

There are two main findings in the present study. The first is that the serum AP-13 level was significantly lower in the CAE group compared with the CAD group and control group, and the second is that HDL-c and AP-13 were independent risk factors for CAE. To the best of our knowledge, this is the first research to demon-

Table 1. Clinical characteristics of the study groups

	Normal (n = 50)	CAD (n = 50)	CAE (n = 40)	p value
Age (years)	58.06 ± 9.51	62.08 ± 8.29	61.28 ± 8.46	0.510
Gender (M), n (%)	15 (21.4%)	29 (41.4%)	26 (37.1%)	0.002
BMI (kg/m^2)	25.02 ± 1.63	25.50 ± 2.38	25.17 ± 1.48	0.232
DM, n (%)	11 (26.2%)	19 (45.2%)	12 (28.6%)	0.201
Hypertension, n (%)	30 (33.3%)	32 (35.6%)	28 (32.1%)	0.615
Alcohol, n (%)	18 (33.3%)	19 (35.2%)	17 (31.5%)	0.156
Smoking, n (%)	16 (33.3%)	17 (35.4%)	15 (31.3%)	0.860
Family history of CAD, n (%)	14 (32.6%)	19 (44.2%)	10 (23.3%)	0.126
Previous medications				
Aspirin, n (%)	18 (28.6%)	23 (36.5%)	22 (34.9%)	0.195
b-blocker, n (%)	32 (35.2%)	36 (39.6%)	23 (25.3%)	0.352
CCB, n (%)	12 (28.6%)	16 (38.1%)	14 (33.3%)	0.490
ACEI/ARB, n (%)	26 (36.6%)	21 (29.6%)	24 (33.8%)	0.231
Statin, n (%)				
Hypoglycemic agents, n (%)	8 (28.6%)	11 (39.3%)	9 (32.4%)	0.677

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blockers; DM, diabetes mellitus.

Table 2. Laboratory findings of the study groups

	Normal (n = 50)	CAD (n = 50)	CAE (n = 40)	p value	Comparison between groups		
					P1	P2	P3
White blood cell	6.45 ± 1.76	6.78 ± 1.50	7.02 ± 1.66	0.255			
Lymphocyte	25.47 ± 7.36	27.01 ± 7.97	25.20 ± 7.55	0.773			
TG (mmol/L)	1.58 ± 0.81	2.11 ± 1.37	1.79 ± 0.88	0.046	0.014	0.360	0.155
TC (mmol/L)	4.54 ± 0.80	4.70 ± 1.44	4.40 ± 1.16	0.470			
HDL-c (mmol/L)	1.24 ± 0.21	1.11 ± 0.26	1.03 ± 0.19	< 0.001	0.007	< 0.001	0.084
LDL-c (mmol/L)	2.92 ± 0.72	3.11 ± 1.17	2.90 ± 1.05	0.545			
VLDL-c (mmol/L)	0.72 ± 0.37	0.95 ± 0.62	0.82 ± 0.40	0.051			
HS-CRP (mg/L)	1.05 (0.73, 1.91)	1.55 (0.83, 2.76)	1.05 (0.66, 2.93)	0.255			
Creatinine (μmol/L)	59.96 ± 13.70	61.88 ± 14.71	66.05 ± 14.07	0.126			
Homocysteine (μmol/L)	9.52 ± 2.31	13.67 ± 6.17	12.69 ± 7.05	0.001	< 0.001	0.007	0.398
Cystatin C (mg/L)	0.81 ± 0.13	0.84 ± 0.16	0.88 ± 0.20	0.122			
Blood glucose (mmol/L)	5.53 ± 1.48	6.18 ± 1.71	6.51 ± 2.08	0.027	0.066	0.010	0.381
Blood uric acid (μmol/L)	292.14 ± 65.95	294.88 ± 74.17	329.38 ± 105.98	0.068			
Apelin-13 (ng/mL)	3.12 ± 1.64	2.49 ± 1.19	1.86 ± 0.59	< 0.001	0.079	< 0.001	0.004

p values less than 0.05 are in bold. p values for comparison among groups and between groups: P1, control group vs. CAD group; P2, control group vs. CAE group; P3, CAD group vs. CAE group.
Significance level was set to 0.05.
CAD, coronary artery disease; CAE, coronary artery ectasia; HDL-c, high-density lipoprotein cholesterol; HS-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; VLDL-c, very low-density lipoprotein cholesterol.

Table 3. Logistic regression analysis of the variables

	B	S.E.	Wals	df	p value	Exp (B)	Exp (B) 95% CI	
							Lower	Upper
Gender	0.639	0.631	1.024	1	0.311	1.894	0.550	6.527
HDL-c	-6.830	1.906	12.840	1	< 0.001	0.001	0.000	0.045
HCY	0.161	0.088	3.372	1	0.066	1.175	0.989	1.395
TG	-0.458	0.412	1.235	1	0.266	0.633	0.282	1.418
GLU	0.191	0.167	1.310	1	0.252	1.211	0.873	1.681
Apelin-13	-1.151	0.359	10.258	1	0.001	0.316	0.156	0.640

B, regression coefficient B; CI, confidence interval; df, degrees of freedom; Exp (B), exp-function of regression coefficient B, is also called odds ratio; HCY, homocysteine; HDL-c, high-density lipoprotein cholesterol; GLU, blood glucose; S.E., standard error; TG, triglycerides.

strate a link between AP-13 and CAE. Coronary artery ectasia refers to the localized or diffuse expansion of the coronary arteries to 1.5 times the normal range,[13] and the coronary artery is usually compared with adjacent or dissected vessels. More than 50% of CAE patients have coronary heart disease,[14] and approximately 20% of patients with CAE do not have accompanying coronary stenosis or other cardiovascular diseases, which is called isolated coronary ectasia.[15] According to its different primary factors, CAE can be roughly divided into three groups. The first group includes patients with both coronary heart disease and CAE, and such patients are the most common. Approximately 50% of CAE patients have different degrees of coronary artery stenosis with lesions. The second group includes patients with CAE caused by rheumatoid immunological diseases and is characterized by ectasia of coronary artery aneurysms. Common primary diseases include Kawasaki disease, systemic arteritis and systemic lupus erythematosus. The third group includes patients with simple CAE, also known as isolated CAE, which refers to a change in CAE without obvious underlying disease. The prevalence of

such patients is low, and these patients account for approximately only 0.08% to 0.10% of all CAG patients.[16]

Despite increasing attention being paid to CAE, the etiology and pathogenesis of CAE are not clear. At present, the hypothesized mechanisms of CAE pathogenesis include inflammatory vascular hypothesis, enzymatic degradation of the arterial wall elastic layer, endothelial dysfunction, and genetic factors. According to the inflammatory vascular hypothesis, the existence of CAE is related to elevated levels of inflammatory mediators such as high-sensitivity C-reactive protein (hsCRP),[17] tumour necrosis factor α (TNF-α),[18] interleukin-6 (IL-6),[19] adiponectin,[20] intercellular adhesion molecules,[21] vascular cell adhesion molecules,[21] and E-selectin.[21] This hypothesis suggests that patients with CAE have a wide range of inflammatory states. In recent years, many studies have confirmed the close relationship between Apelin and inflammatory mediators. In the study by Elshehaby et al.,[22] the Apelin level in CAE patients was negatively correlated with the level of inflammatory markers (hsCRP and IL-6). Leeper et al.[23] reported that Apelin infusion could significantly reduce the levels of IL-6 and TNF-α messenger RNA in the aorta and prevent aneurysm formation by inhibiting macrophage proinflammatory cytokines. This indirectly suggests that Apelin may be involved in the occurrence and development of CAE.

In patients with CAE, the intima of dilated arteries is intact, but there is extensive media degeneration and hyalinization. One possible mechanism of CAE is the hydrolysis of extracellular matrix proteins by metalloproteinases (MMPs). The overexpression of MMPs, and especially MMP-3, can lead to enhanced vascular wall degradation of various matrix proteins. Therefore, the overexpression of MMPs may lead to excessive vascular wall dilation. Loss of the elastic layer components in the vascular wall plays an important role in the pathogenesis of CAE. CAE, and especially non-atherosclerotic CAE, is characterized by thinning of vessel walls, and vascular wall thinning is caused by degeneration of vascular wall mediators and replacement of smooth muscle by hyaluronic collagen. Li et al.[24] reported that Apelin may have a regulatory effect on the proliferation and migration of vascular smooth muscle cells. In addition, Wang et al.[25] found that AP-13 could overexpress MMP-2 by activating the PI3K/Akt/FoxO3a/MMP-2 pathway, thus promoting the migration of vascular smooth muscle cells (VSMC).

The Apelin-APJ system is highly expressed in cardiac ventricular myocytes and vascular tissues such as endothelial cells and vascular smooth muscle cells.[26,27] Apelin has been demonstrated to have many functions, including dilation of blood vessels, decrease in blood pressure,[10] enhanced myocardial contractility[28] and myocardial protection.[29] A recent study showed a negative correlation between serum Apelin levels and the severity of calcified aortic stenosis.[30] This suggests that Apelin plays an important role in the pathological process of vascular remodeling. Apelin dilates the arteries and veins and has a vasodilation effect. By activating endothelial endothelial NOS (eNOS) of endothelial cells, the mechanism stimulates the production and release of nitric oxide (NO).[31,32] In the process of coronary atherosclerosis, endothelial cell damage, and renin-angiotensin system (RAS) system activation, AngII promotes the role of vascular smooth muscle cell migration, proliferation and apoptosis, and promotes the formation of atherosclerotic plaque. Chun et al.[33] found that AP-13 was induced by blocking AngII neointimal formation and vascular remodeling, thus inhibiting the formation of coronary atherosclerosis. In this study, serum AP-13 levels in the CAD and CAE groups were lower than those in the normal control group, suggesting that serum AP-13 levels may be involved in the process of atherosclerosis and formation of CAE. A large number of studies have shown that coronary artery stenosis is characterized by progressive inflammatory cell infiltration, lipid deposition and fibrosis. We hypothesize that AP-13, as a cardiovascular protective factor, would be continuously expressed during the course of coronary atherosclerosis to fight the angiotensin II constriction of blood vessels. At the same time, endothelial cells activate endothelial eNOS and stimulate the production and release of NO to relax blood vessels. Recently, Mughal et al. reported the NO-dependent dilatation mechanism of Apelin-induced coronary artery in rats, thereby confirming our conjecture.

The main role of HDL-c is to transport TC from the surrounding tissues of the body to the liver for lipid metabolism, which effectively avoids deposition of lipids in the blood vessel wall. Cekici et al.[34] reported a correlation between blood viscosity and CAE. Blood viscosity affects changes in blood lipids. In the present study, the serum HDL-c level of patients in CAE group was signifi-

cantly lower than that in the control group. A sustained decrease in HDL-c may lead to an increase in serum free TC, thus further damaging the coronary system. A previous study by Harun et al.[35] on blood lipid detection in CAE patients also suggested that a low HDL-c level is highly correlated with CAE.

Limitations

The main limitation of this research is that the included sample was too small. Although sample size calculation showed that 42 cases in each group was sufficient, multi-center and large-sample studies are still needed to confirm the relationship between AP-13 and CAE.

CONCLUSIONS

In this research, we found that the patients with CAE had elevated serum AP-13 levels compared to levels in the patients with CAD. According to our findings, we suggest that AP-13 plays an important role in the development of CAE. In addition, we found that AP-13 and HDL-c were independent risk factors for CAE.

DECLARATION OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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