THE RELATIONSHIPS OF ISOLATED CORONARY ARTERY ECTASIA WITH UROTENSIN 2 LEVELS, HYPERTENSION AND OTHER ATHEROSCLEROTIC RISK FACTORS

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ABSTRACT

Aims*: Isolated coronary artery ectasia (ICAE) is characterized with ectasia of the coronary arteries due to inflammation, atherosclerosis and positive vascular remodelling without concomitant stenosis. Urotensin II (UII) is an important vascular peptide which has influence on vascular remodelling in addition to potent vasoconstrictor effect. We investigated UII levels, hypertension, and other atherosclerotic risk factors in patients with ICAE.*

Materials and methods*: Among 1820 patients who underwent coronary angiography between May 2010 and 2011 in our hospital, 20 patients (18 male) with ICAE, and 28 patients (11 male) with normal coronary arteries (NCA) were enrolled. We compared UII levels, risk factors between patients with ICAE and NCA.*

Results*: UII concentrations were significantly higher in patients with ICAE compared to controls (700.0±16.6 ng/ml vs. 708.0±33.5 ng/ml, p:0.02). Moreover, patients with ICAE tended to be older, with higher BMI, lower high density lipoprotein cholesterol (HDL-C) and more prevalent hypertension. ICAE correlated positively with UII levels (r:0.339, p:0.02), advanced age (r:0.594, p: 0.001), BMI (r:0.390, p: 0.005) whereas a negative correlation existed between HDL-C, and ICAE (r:-0.305, p:0.037).*

Conclusion*: We identified increased UII levels in patients with ICAE. Higher UII concentrations may further imply the role of atherosclerosis in ICAE pathogenesis due to its relationship with inflammation, atherosclerosis and vascular remodelling.*

Key words*: Isolated coronary artery ectasia, atherosclerosis, vascular remodelling, hypertension, Urotensin II, atherosclerotic risk factors.*

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Introduction

Coronary artery ectasia (CAE) is characterized with diffuse or segmental dilatation of the coronary artery exceeding 1.5 times greater than the normal adjacent vessel diameter[1]. Half of the cases have concomitant atherosclerotic stenosis. CAE is due to congenital reasons in 20-30% of the patients[2-4]. The prevalence of isolated CAE (ICAE) has been reported to be 1.2-4.9 % in various studies[1-5]. The etiology and clinical course of ICAE has not been understood clearly. Markis et al. stated that the histological alterations of ICAE were similar to observed findings in atherosclerotic plaques, such as hyalinization, diffuse intimal and medial degeneration[6]. However, due to discrepancy of patient characteristics with coronary artery disease and CAE, different physiopathological causes were also investigated. Thrombus, vasospasm and slow flow in coronary arteries have also been reported in patients with CAE[7].

Histopathological alterations in coronary artery ectasia have many resembling features with coronary atherosclerosis. Histological examination of the ectatic segments revealed diffuse atherosclerotic alterations and disruption of the vascular media layer[8].

Urotensin II (UII), an undecapeptide cleaved from a precursor protein, promotes vasoconstriction and vascular smooth muscle cell proliferation[9,10]. UII is one of the most important and most studied peptides involved in vascular remodelling.

Increased UII concentrations have been demonstrated in patients with hypertension and atherosclerosis, implicating a role of its vasoconstrictor actions in these pathologies[11, 13].

Even though the pathophysiologic impact of UII in atherosclerosis and coronary artery disease has been studied extensively, the role UII in ICAE as a different variety of atherosclerosis has not been investigated so far. Therefore, we intended to investigate UII concentrations, and atherosclerotic risk factors in patients with ICAE compared to controls.

Material and method

Study design and patient population

Forty patients with type 2 DM, 40 with obesityOur study was prospective and cross-sectional. Among 1820 patients who underwent coronary angiography due to suspicion of coronary artery disease between May 2010 and 2011 in our hospital, 20 patients (18 male) with ICAE (1.9%) were enrolled for study group. Control group consisted of 28 patients (11 male) who underwent coronary angiography within the same period and had normal coronary angiograms. The study was approved by the local ethics committee and was in accord with the Declaration of Helsinki. All patients gave informed consent before participation. Medical histories were taken and thorough examination was performed. UII levels were measured in all subjects and compared between groups.

Patients with obstructive coronary artery disease, left ventricular dysfunction, left ventricular hypertrophy, atrial fibrillation, valvular heart disease, pericardial and myocardial diseases, renal dysfunction (creatinine >1.5mg/dL), anaemia, thrombocytopenia, hepatic dysfunction, neoplasms, recent major surgical operation, and accompanying inflammatory diseases such as haemolytic and autoimmune disorders were excluded.

Presence of typical angina pectoris and positive or equivocal results in non-invasive stress tests were the indications for coronary angiography. Hypertension was acknowledged if the patient was on antihypertensive medication or if systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or both were observed during examination. Diabetes mellitus was considered if fasting glucose was >126 mg/dl or if the patient was on antidiabetic therapy. The patients who smoke ≥ 10 cigarettes per day were considered to be smokers.

Determination of isolated coronary artery ectasia

Coronary angiography was performed with 6 French left and right coronary catheters, using standard Judkins technique without the use of nitroglycerin. Coronary angiograms were analysed by two blinded experts. Coronary artery ectasia (CAE) was defined as dilatation of the coronary artery lumen exceeding 1.5 times greater than the normal adjacent vessel diameter[14].

Biochemical Analyses and Measurement of Urotensin II

We collected blood samples from the antecubital vein of subjects after overnight fasting to measure blood biochemical parameters, including plasma UII levels. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods.

Plasma was separated by low-speed (2500 x g) centrifugation for 15 min. Plasma levels of Urotensin II was measured by an enzyme linked immunoassay (EIA) method[1]. A specific and sensitive EIA kit was used for this assay (PhoenixPharmaceutical Inc., California, USA). The intra and inter-assay coefficients of variations were <15% and <5%, respectively. The minimum detectable concentration was 0.06 ng/mL.

Statistics analyses

The statistical package for the social sciences (SPSS) statistical software (SPSS 15.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean ± standard deviation (SD); categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov-Smirnov test. The Student's t-test was used for the univariate analysis of normally distributed continuous numerical variables and Mann-Whitney U-test was used for non-normally distributed numerical variables, and the $\chi 2$-test for the categorical variables. All tests of significance were two-tailed. Statistical significance was defined as $P<0.05$

Results

Patient characteristics

20 patients (18 male) with ICAE (1.9%) were enrolled for study group. Control group consisted of 28 patients (11 male) who underwent coronary angiography within the same period and had normal coronary angiograms.

Risk factors and biochemistry analyses

UII concentrations were significantly higher in patients with ICAE compared to controls (700.0±16.6, 708.0±33.5, p:0.02). Moreover, patients with ICAE tended to be older (58 ± 10 vs. 52 ± 9, p: 0.001), with higher body mass index (BMI) (30±5 vs. 27±4, p: 0.005), lower high density lipoprotein cholesterol (HDL-C) (40±8 vs 44±12 mg/dL, p:0.037), and more prevalent hypertension (60% vs. 11%, p: 0.001).

Parameters (N=47)	ICAE (N=20)	Control group (N=28)	P value
Age (years± SD)	58 ± 10	52 ± 9	0.001
Sex (male), n (%)	18 (90)	11 (40)	0.001
Body Mass Index (kg/m2)	30 ± 5	27 ± 4	0.005
Hypercholesterolemia , n (%)	10 (50)	10 (35)	0.3
Family history of CAD , n (%)	7(35)	9 (32)	0.8
Smoking, n (%)	8 (40)	8 (29)	0.4
HT, n (%)	12 (60)	3 (11)	0.001
Diabetes mellitus, n (%)	5 (25)	4 (14)	0.35
Hemoglobin (gr/dl)	14.1±1.4	13.7±1.3	0.2
Glucose (mg/dl)	99±38	97±10	0.4
Total Cholesterol (mg/dl)	193±39	199±38	0.5
LDL-Cholesterol (mg/dl)	117±32	128±30	0.8
HDL-Cholesterol (mg/dl)	40±8	44±12	0.037
Triglycerides (mg/dl)	191±132	158±78	0.1
CRP (mg/dl)	0.45±0.33	0.44±0.33	0.9
Urotensin II (ng/ml)	708.0±33.5	700.0±16.6	0.02

Table 1: Baseline characteristics of the study population.
ICAE, Isolated coronary artery ectasia; UII, Urotensin II levels, HT, Hypertension; SD, standard deviation; NCA, Normal coronary artery (Control group); CAD, Coronary artery disease; CRP, c reactive protein; LDL, Low-density lipoprotein; HDL, High-density lipoprotein. The Student's t-test was used for the univariate analysis of normally distributed continuous numerical variables and Mann-Whitney U-test was used for non-normally distributed numerical variables, and the χ2-test for the categorical variables.

Remaining basal characteristics and serum high sensitive C reactive protein (hsCRP) concentrations were similar between groups. ICAE correlated positively with UII levels (r:0.339, p:0.02), advanced age (r:0.594, p: 0.001), and BMI (r:0.390, p: 0.005) whereas a negative correlation existed between HDL-C, and ICAE (r:-0.305, p:0.037) (Tables 1-2 and Figures 1).

Parameters	ICAE	Age	U II	HT	BMI	HDL
ICAE	-	r=0.594	r=0.339	r=0.524	r=0.390	r=-0.305
		p=0.001	p=0.02	p=0.001	p=0.006	p=0.037
Age	r=0.594	-	r=0.285	r=0.610	r=0.389	r=0.003
	p=0.001		p=0.052	p=0.001	p=0.006	p=0.986
U II	r=0.339	r=0.285	-	r=0.279	r=0.102	r=-0.233
	p=0.02	p=0.052		p=0.057	p=0.491	p=0.115
HT	r=0.524	r=0.610	r=0.279	-	r=0.355	r=-0.084
	p=0.001	p=0.001	p=0.057		p=0.013	p=0.574
BMI	r=0.390	r=0.389	r=0.102	r=0.355	-	r=-0.140
	p=0.006	p=0.006	p=0.491	p=0.013		p=0.349
HDL	r=-0.305	r=0.003	r=-0.233	r=-0.084	r=-0.140	-
	p=0.037	p=0.986	p=0.115	p=0.574	p=0.349	

Table 2: Correlations of study parameters with ICEA and UII.
ICAE, Isolated coronary artery ectasia; UII, Urotensin II levels, HT, Hypertension; BMI, Body mass index, HDL, High-density lipoprotein. Pearson& Spearmen tests were used to analyze the relationship between catestatin and study variables where appropriate.

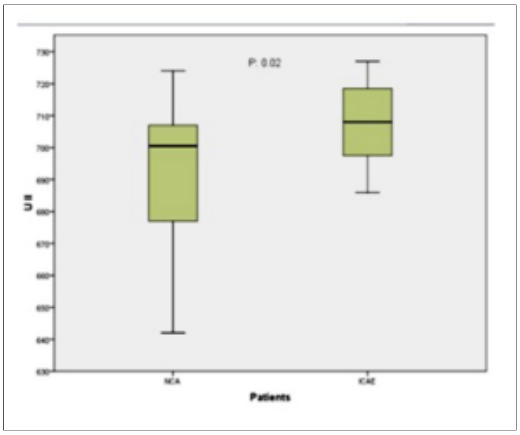

Fig. 1: Comparison of urotensin II levels between ICAE and NCA groups.
ICAE, Isolated coronary artery ectasia; UII, Urotensin II levels, NCA, Normal coronary artery

Discussion

In the present study, we demonstrated significantly higher UII levels in patients with isolated coronary artery ectasia (CAE) compared with

patients with angiographically normal coronary arteries. To our knowledge, this is the first report demonstrating the relationship of ICEA with increased UII levels. Moreover, we detected that CAE significantly associated with hypertension, low HDL-C, advanced age and obesity.

Controversy still exists regarding the mechanisms and processes that take place in the pathogenesis of CAE. Frequent coexistence of CAE and coronary artery disease (CAD) and the histopathological findings that resemble those of atherosclerosis have allowed the conclusion that atherosclerosis may have a role in the pathogenesis, and CAE may be a variant of atherosclerosis related to positive remodelling described as the enlargement of the area within the external elastic membrane.

However, there are several unknown aspects, such as why some patients with CAD have CAE while remaining most do not, and why CAE is related to other disorders such as collagenosis, connective tissue diseases, and vasculitis[14].

Interestingly, serum C reactive protein (CRP) levels did not differ between groups. We may hypothesize that CRP may not be as sensitive as UII for detection of slow atherosclerotic process and low-grade inflammation that take place in CAE pathogenesis.

Urotensin II induces potent vasoconstriction and vascular smooth muscle cell proliferation. The urotensin II receptor- urotensin II interaction stimulate release of calcium in vascular smooth muscle cells through inositol triphosphate and diacylglycerol. Increased intracellular calcium concentrations lead to cellular proliferation and activation of Ca2+-dependent kinases via calmodulin binding[15].

Recent studies have shown that Urotensin II may have additional influence on vascular remodelling. UII and angiotensin II affect vascular endothelial growth factor (VEGF) expression in adventitial fibroblasts that play an important role in vascular remodelling. Although the exact role of VEGF in vascular remodelling induced by UII is still not clarified, adventitial fibroblast proliferation and increased collagen synthesis may ensue[16].

Since UII is related to atherosclerosis, the association between UII and ICAE, a specific variety of atherosclerosis, is also plausible. Moreover, CAE resembles atherosclerosis and frequently co-exists with atherosclerotic lesions (plaque, stenosis). Thus, one may conclude that atherosclerosis has a pivotal role in the pathogenesis, and CAE is a variant of atherosclerosis related to positive remodelling described as the enlargement of the area within the external elastic membrane[17]. We also demonstrated that CAE related with hypertension, low HDL-C, advanced age and obesity, all of which are risk factors of atherosclerosis.

Studies investigating the association between UII and atherosclerosis have revealed elevated plasma UII levels in patients with atherosclerosis and coronary artery disease. UII is synthesized in endothelial cells, smooth muscle cells and infiltrating macrophages of atherosclerotic lesions. Inflammation up-regulates urotensin receptor expression Stimulation of receptor by UII leads to endothelial and smooth muscle cell proliferation, and chemotaxis[18]. In addition to heart, brain, kidney, vascular smooth muscle cells, and endothelium, both UII and the receptor are expressed in atherosclerotic plaques of the coronary and carotid arteries, and abdominal aortic aneurysms, specifically at the regions of monocyte/macrophage infiltration[19-21].

Data suggest that UII concentrations not only reflect atherosclerosis but also relate to extent. Plasma UII levels correlated with the severity of coronary artery disease in patients with stable angina pectoris. Moreover, UII levels were significantly higher in patients with triple-vessel disease than in healthy volunteers or patients with single- or double-vessel disease[22]. Elevated UII concentrations were also detected in patients with hypertension[23,24].

We demonstrated elevated UII levels in patients with ICAE and revealed significant association of several atherosclerotic risk factors with ICAE. Since UII is a marker of inflammation and atherosclerosis severity, elevated UII may confer an additional risk in this seemingly low risk condition. UII concentrations may be informative on ICAE pathogenesis due to relationship with inflammation, atherosclerosis and vascular remodelling.

Study limitations

This study was carried out in a relatively limited number of patients. In the current study, the patients did not undergo IVUS (intravascular ultrasonography) to detect whether there was positive atherosclerotic remodelling in ectatic arteries. Hence, the coexistence of non-obstructive CAD (<40%) in patients with "isolated" CAE cannot be established absolutely. Nevertheless, in clinical practice, isolated CAE patients do not undergo IVUS routinely and coronary artery ectasia is usually diagnosed with visual assessment of coronary angiography.

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