

Evaluation of the Serum Levels of Uric Acid and C-reactive Protein in Isolated Coronary Artery Ectasia



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ABSTRACT

Introduction: Isolated coronary artery ectasia (CAE) is defined as the arterial enlargement of 1.5 times or more compared to the adjacent normal arterial portion without significant coronary artery stenosis. Although the exact cause is not clearly known, increased inflammation is the most responsible factor in pathogenesis of CAE. Serum uric acid (SUA) and C-reactive protein (CRP) are the most widely used markers of inflammation. In this study, we aimed to investigate the possible association of isolated CAE with SUA and CRP levels.

Patients and Methods: In this study, 4.600 patients undergoing coronary angiography in our hospital due to a known or suspected ischemic heart disease between January 2011 and August 2012 were retrospectively evaluated. Following the exclusion criteria, our study population consisted of 110 (63.6% males, mean age: 58.1±9.5 years) isolated CAE patients, 110 patients (63.6% males, mean age: 55.2±2.3 years) with coronary artery diseases (CAD) who were matched with this group in age, gender and cardiovascular risk factors (body mass index, hypertension, diabetes, hyperlipidemia and smoking status) and 100 patients with angiographically normal coronary arteries (51.0% males; mean age: 57.6±10.1 years). Basal SUA and CRP are routinely measured in our clinic before the coronary angiography.

Results: Serum level of uric acid did not show a significant difference between CAE and CAD groups (6.5±0.5 mg/dL and 6.4±0.5 mg/dL; p>0.05), while this value was found significantly higher in both groups compared to the controls (5.1±0.5 mg/dL; p<0.001). Similarly, there was not a significant difference between CAE and CAD groups in terms of the serum level of CRP (1.8±0.0 mg/dL and 1.7±0.3 mg/dL; p>0.05), while CRP values were significantly higher in both groups compared to the controls (1.1±0.4 mg/dL; p<0.001).

Conclusion: We found that levels of SUA and CRP were higher in the patients with CAE than in subjects with normal coronary artery, but no significant different was found compared to patients with CAD. These data suggest that both CAE and CAD shared common pathophysiological mechanisms.

Key Words: Coronary ectasia; coronary artery disease; serum uric acid; C-reactive protein

İzole Koroner Arter Ektazilerinde Serum Ürik Asit ve C-reaktif Protein Düzeylerinin Değerlendirilmesi

ÖZET

Giriş: İzole koroner arter ektazileri (KAE) ciddi koroner arter darlığı olmaksızın normal koroner arter bölgesine göre 1,5 kat veya daha fazla arter genişlemesi olarak tanımlanır. KAE'nin nedeni tam olarak bilinmemekle beraber patogenezinde en çok artmış inflamasyon suçlanmaktadır. Serum ürik asit (SUA) ve C-reaktif protein (CRP) inflamasyonun yaygın kullanılan belirteçleridir. Biz bu çalışmada SUA ve CRP ile izole KAE arasındaki muhtemel ilişkiyi araştırdık.

Hastalar ve Yöntem: Bu çalışmada bilinen veya şüpheli iskemik kalp hastalığı nedeniyle Ocak 2011-Ağustos 2012 tarihleri arasında hastanemizde koroner anjiyografi yapılan 4600 hasta geriye dönük olarak değerlendirildi. Dışlanma kriterleri sonrası, çalışma popülasyonumuz 110 (Erkek, 63,6%; ort. yaş, 55,1±2,5 yıl) izole KAE hastası, bu grupta yaş, cinsiyet ve kardiyovasküler risk faktörleri (vücut kütle indeksi, hipertansiyon, diyabet, hiperlipidemi ve sigara içiciliği) olarak eşlenmiş 110 koroner arter hastası (KAH) (Erkek, 63,6%, ort. yaş, 55,2±2,3 yıl) ve 100 anjiyografik olarak normal koroner arterlere sahip hastayı (Erkek, 63,6%, ort. yaş, 55,2±2,5 yıl) kapsadı.

Bulgular: Serum ürik asit düzeyi KAE ve KAH grupları arasında anlamlı fark göstermezken (6,5±0,5 mg/dl ve 6,4±0,5 mg/dl; p>0,05), kontrol grubuna (5,1±0,5 mg/dl) göre her iki grupta da anlamlı derecede yüksek bulundu (p<0,001). Benzer şekilde serum CRP düzeyi KAE ve KAH grupları arasında anlamlı fark göstermezken (1,8±0,0 mg/dl ve 1,7±0,3 mg/dl; p>0,05), kontrol grubuna (1,1±0,4 mg/dl) göre her iki grupta da anlamlı derecede yüksek bulundu (p<0,01).

Sonuç: KAE olanlarda, normal koroner arterlere sahip olanlar ile karşılaştırıldığında, SUA ve CRP seviyelerinin yüksek olduğunu ancak KAH ile karşılaştırıldığında anlamlı farklılık olmadığını saptadık. Bu veriler, KAE ve KAH'ın ortak patofizyolojik mekanizmaya sahip olduğunu düşündürmektedir.

Anahtar Kelimeler: Koroner ektazi; koroner arter hastalığı; serum ürik asit; C-reaktif protein

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INTRODUCTION

Coronary artery ectasia (CAE), an abnormality of the coronary anatomy, has been identified as an enlarged artery luminal diameter that is 1.5 or more times greater than the diameter of the adjacent normal portion of the artery⁽¹⁾. Isolated CAE is defined as coronary artery ectasia developed without a significant coronary artery stenosis. In the previous studies, CAE was shown to be associated with the increased risk for cardiovascular events⁽²⁾. The underlying mechanisms responsible for ectasia formation are not clearly known, but previous studies have reported that CAE may be a form of atherosclerosis and has more potent inflammatory properties than normal vessels^(3,4).

Uric acid is the final breakdown product of purine metabolism. Numerous studies have demonstrated that serum level of uric acid (SUA) is an important and independent risk factor for development of cardiovascular diseases⁽⁵⁻⁷⁾. Significant correlations have been reported between SUA and the conditions inducing or accelerating atherosclerosis such as various inflammatory markers, oxidative stress and endothelial dysfunction⁽⁸⁻¹¹⁾.

C-reactive protein (CRP) is a member of the pentraxin groups, consisting from the discoid pentameric structures. While initially it was believed to be arised merely from the liver, later it was demonstrated to be produced also in adipocytes, atherosclerotic lesions, coronary artery smooth cells and aortic endothelial cells⁽¹²⁻¹⁵⁾. Increased CRP, as a significant marker of inflammation, is known to be correlated with endothelial dysfunction and atherosclerotic formation⁽¹⁶⁾.

Given that the mechanism of CAE to be associated with an increased inflammation and CRP and SUA are markers of inflammation, we hypothesized that increased CRP and SUA might be associated with the presence of isolated CAE. We evaluated this hypothesis in a real world population of patients who underwent coronary angiography for suspected or known ischemic heart disease.

PATIENTS and METHODS

Patient Selection

Four thousand six hundred patients who underwent coronary angiography due to suspected or known ischemic heart disease between January 2011 and August 2012 were retrospectively evaluated. A hundred and ten patients (2.9%) with CAE were identified (group 1, 63.6% male; mean age 55.1±2.5). A hundred and ten consecutive patients matched with CAE in terms of age, sex and cardiovascular risk factors (63.6% male, mean age 55.2±2.3) were assigned to group 2, and a hundred patients with angiographically normal coronary arteries constituted the control group (group 3, 51% male; mean age 55.2±2.5).

Presence of hypertension was considered as a systolic blood pressure of 140 mmHg or higher, a diastolic pressure of 90 mmHg or higher or using antihypertensive medications. Diabetes mellitus was defined as having a fasting blood glucose of 126 mg/dL or higher or currently receiving antidiabetic therapy or being on diet.

Typical angina or a positive or suspected outcome yielded by one of the non-invasive methods for coronary arterial examination was defined as an indication for coronary angiography. Body mass index (BMI), glucose, triglycerides, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) of the patients were measured. Smoking habit was determined. Our study was approved by the local ethics committee.

Evaluation of Coronary Artery Ectasia and Coronary Artery Disease

Coronary angiography was carried out according to Judkins technique with 6 Fr right and left heart catheters without nitroglycerin use. Angiograms were recorded into the digital media with a rate of 25 frame/milliseconds and evaluated by two angiography specialists who were unaware of the patient's data. Coronary artery ectasia was defined as the enlargement of coronary artery by 1.5 times or more compared to the adjacent normal coronary artery. Stenosis of 20% or more in at least one vessel was defined as coronary artery disease (CAD).

Laboratory

Blood samples are collected from antecubital vein by an atraumatic puncture prior to the coronary angiography and sent to the laboratory for analysis within 1 hour after collection.

Definition of the Serum Level of C-reactive Protein

Blood samples were collected from one of the antecubital veins without venous stasis and taken into tubes which did not contain sterile and anticoagulant. Serum CRP concentrations were measured with nephelometric Siemens Dade-Behring NBII device (Siemens Healtycare Diagnostics Products GmbH, Marburg/Germany).

Definition of the Serum Level of Uric Acid

Blood samples were collected from the patients with a fasting for one night prior to coronary angiography and then the samples were centrifuged at 3000 g for 10 minutes. The samples were kept at -70 °C and then analyzed. Serum level of uric acid was measured in a clinical chemistry autoanalyzer (Modular P, Roche Diagnostics, Germany-Switzerland) using enzymatic colorimetric assay.

Statistical Method

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. Adequacy of all parameters to normal distribution, was tested by using Kolmogorov-Smirnov Test. To compare parametric continuous variables, the Student's t test or ANOVA were used; to compare nonparametric continuous variables, the Mann-Whitney U or Kruskal-Wallis were used; to compare categorical variables, the chi-square test was used. Effect level was analyzed using logistics regression and Receiver Operating Characteristics (ROC) curve. Pearson and Spearman correlation analyses were used for the correlation analysis. Two-tailed p values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS, version 20.0 for Windows.

RESULTS

Among 320 patients (mean age 55.1 ± 2.6 ; 59.4% male), SUA ranged from 3 to 7.6 mg/dL (mean 6 ± 0.5 mg/dL) and CRP ranged from 0.5 to 2.4 mg/dL (mean 1.3 ± 0.2 mg/dL). The baseline characteristics of all groups are summarized in Table 1.

In CAD group, CAD was identified to affect the left anterior descending artery the most (72.5%), followed by circumflex (61.7%) and right coronary artery (55.5%). Additionally, CAD was found to have a tendency to affect 1-vessel (57%), 2-vessel (33%), and 3-vessel (10%), respectively.

Uric acid and CRP values were significantly lower ($p < 0.05$) in normal coronary artery patients compared to patients with CAE and CAD. Uric acid and CRP values were similar in the patients with CAE and CAD ($p > 0.05$) (Table 2, Figure 1).

In the one-variable logistic regression analysis, uric acid value created a significant model and increased the odds for coronary ectasia by 2.583 folds (147-45314) ($p = 0.000 < 0.001$). In the one-variable logistic regression analysis, CRP value created a significant model and increased the odds for coronary ectasia by 1.187 folds (182-7735) ($p < 0.001$) (Table 3).

In multivariable logistic regression, effect of uric acid was found to be significant, while effect of the CRP level was not significant. Uric acid value was an independent risk factor (Table 4).

A positive correlation was found between the levels of CRP and uric acid (Figure 2).

The most effective cut-off value distinguishing a patient with coronary ectasia from a normal coronary artery patient was 1.5 mg/dL for a CRP level (Area under curve=0.930, $p < 0.001$) (Table 5).

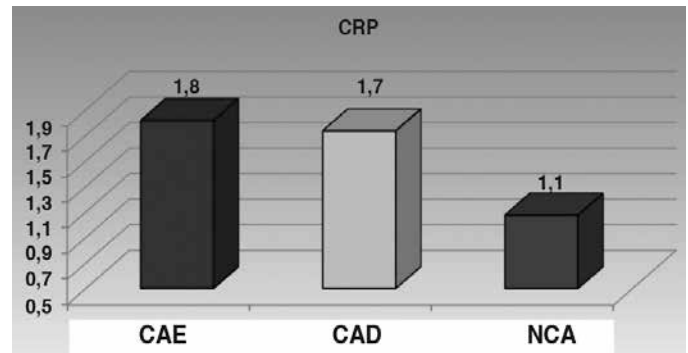


Figure 1. C-reactive protein levels in all groups, CAD: Coronary artery disease, CAE: Coronary artery ectasia, CRP: C-reactive protein, NCA: Normal coronary artery

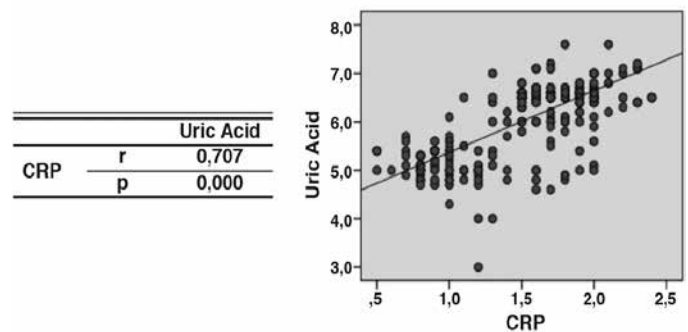


Figure 2. Positive correlation between uric acid and C-reactive protein levels, CRP: C-reactive protein

		Uric Acid	
CRP	r	0,707	
	p	0,000	

Table 1. Baseline characteristics of all groups

	Coronary ectasy Mean \pm SD/n %	Coronary artery patients Mean \pm SD/n %	Normal coronary patients Mean \pm SD/n %	p
Age	55.1 \pm 2.5	55.2 \pm 2.3	55.2 \pm 2.5	0.946
Gender male	70 %63.6	70 %63.6	51 %51	0.102
female	40 %36.4	40 %36.4	49 %49	
Smoker	31 %28.2	41 %37.3	23 %23.0	0.071
Non-smoker	79 %71.8	69 %62.7	77 %77.0	
HT	39 %35.5	44 %40.0	37 %37.0	0.779
DM	28 %25.5	34 %30.9	37 %37.0	0.195
BMI	25.6 \pm 1.4	25.6 \pm 1.4	25.6 \pm 1.4	0.998
HDL	40.4 \pm 2.7	39.9 \pm 3.3	40.1 \pm 3.1	0.669
LDL	121.2 \pm 3.7	119.1 \pm 14.8	122.0 \pm 8.6	0.195
Triglycerides	185.8 \pm 8.5	183.6 \pm 8.9	186.3 \pm 8.9	0.479
Hemoglobin	14.7 \pm 0.7	14.8 \pm 0.8	14.7 \pm 0.7	0.498

Results are expressed as mean \pm SD and percentage. (BMI: Body mass index, DM: Diabetes mellitus, HDL: High-density lipoprotein cholesterol, HT: Hypertension, LDL: Low-density lipoprotein cholesterol)

Table 2. Plasma uric acid and C-reactive protein (CRP) levels

	Coronary Ectasy Mean \pm SD	Coronary Artery Disease Mean \pm SD	Normal Coronary Artery Mean \pm SD	p
Uric acid	6.5 \pm 0.5	6.4 \pm 0.5	5.1 \pm 0.5	< 0.0001
CRP	1.8 \pm 0.0	1.7 \pm 0.3	1.1 \pm 0.4	< 0.0001

The most effective cut-off value distinguishing a patient with coronary ectasia from a normal coronary artery patient was 6 mg/dL for a level of uric acid (Area under curve=0.995 / $p < 0.001$) (Table 6).

DISCUSSION

In this study, we observed that both CAE and CAD patients had significantly higher levels of SUA and CRP than control subjects. Additionally a greater baseline SUA value was independently associated with the presence of isolated CAE.

In the CASS (coronary artery surgery study), the largest study investigating coronary artery ectasy, CAE was found in 978 (4.9%) of 20,087 patients⁽¹⁾. In another study with 3,900 patients examined by coronary angiography, CAE was observed by 5.3%⁽¹⁷⁾. In our study, this rate was found as 2.9%. Some of the possibilities for this discrepancy might be the definition of CAE and inclusion criteria being used and the different angiography indications of the patient population analyzed.

More than 50% of CAE patients have coronary atherosclerosis, but occasionally CAE is seen in association with connective tissue disorders and vasculitides^(18,19). Therefore, this association supports the view of CAE to be a variant of CAD. CAE has been demonstrated to be related with increased cardiac morbidity and mortality by mechanisms such as coronary slow flow, coronary vasospasm, dissection and thrombus formation⁽¹⁸⁻²⁰⁾. Although the underlying mechanisms responsible for ectasia formation are not clearly known, previous studies have showed that inflammation and oxidative stress are closely associated with CAE⁽²¹⁻²⁴⁾. Additionally, It is well-known that elevated inflammatory markers, such as CRP, IL-6, TNF- α and MMP are related with the presence of CAE⁽²³⁻²⁵⁾.

Uric acid is the final destruction product of purine metabolism. Thus, increased serum level of uric acid is a marker of increased oxidative stress and endothelial dysfunction. Allopurinol, which is a xanthine oxidase inhibitor used for treatment of hyperuricemia, was shown to improve brachial artery flow-related dilatation by decreasing oxidative stress, thus endothelial dysfunction⁽²¹⁾. Furthermore, previous studies reported that the presence of CAE is associated with increased oxidative stress and endothelial dysfunction⁽²²⁾. In our study, we demonstrated that the level of SUA significantly increased in CAE patients, similar to CAD

Table 3. One-variable analysis of the levels of uric acid and C-reactive protein

	Odds Ratio	95% Confidence Interval	p
Uric acid	2583.8	147.3-45314.5	< 0.0001
CRP	1187.0	182.1-7735.2	< 0.0001

Table 4. Multi-variable analysis of the levels of uric acid and C-reactive protein

	Odds Ratio	95% Confidence Interval	p
Uric acid	2106.4	14.6-304456.5	0.003
CRP	16782.6	0.1-2742705841.6	0.112

patients, when compared to NCA patients. While oxidative radicals produced after the purine catabolism might induce endothelial dysfunction and CAE formation, the elevated level of SUA, as another product of this destruction, might be an independent marker for the presence of CAE. Koşar et al.⁽²⁶⁾ demonstrated that CAE, which is attributed to atherosclerosis in 50% of cases, is a diffuse rather than a localised disease. Atherosclerosis is an inflammatory disease causing endothelial dysfunction and impaired endothelial-dependent vasodilatation⁽²⁷⁻²⁹⁾. Increasing evidence shows that inflammation plays a role in all the stages of atherosclerosis. CRP, as an inflammatory protein, directly contributes to atherosclerotic process⁽²⁸⁾. In addition, increased atherosclerotic load increases the CRP level. CRP is deposited in the intima of early atherosclerotic lesions and is chemotactic for monocytes⁽²⁸⁾. CRP plays a role in the early atherogenesis through the early monocyte. Numerous trials clearly demonstrated that the increased levels of CRP increases cardiovascular risk⁽²⁶⁻³²⁾, and are of predictive value in development of diabetes and hypertension and, stroke and myocardial infarction independent from the thickness of intima-media^(26,29,30). Although the underlying inflammatory mechanisms are known in CAD, there is a little information about the role of inflammation in the pathogenesis of CAE. Given the conducted histopathological studies on this topic, postmortem histopathological results of CAE patients demonstrated the presence of a more comprehensive and severe vascular inflammation in CAE patients than in CAD. This situation possibly includes all the vascular layers in the coronary circulation and plays a role in pathogenesis of CAE. In a study by Turhan et al.⁽²³⁾ CRP levels were compared between angiographically NCA, CAD and CAE patients, and they demonstrated that CRP level was significantly higher in CAE and CAD groups than in the control group. Similarly, in our study we showed that the serum CRP levels significantly increased in the CAE patients when compared

Table 5. Cut-off values for C-reactive protein in predicting coronary ectasia

	95% Confidence Interval			p
	Area Under the Curve	Minimum	Maximum	
CRP	0.933	0.894	0.971	< 0.001
CRP <1.4 / 1.4 ≤	0.920	0.877	0.963	< 0.001
CRP <1.5 / 1.5 ≤	0.930	0.889	0.971	< 0.001
CRP <1.6 / 1.6 ≤	0.875	0.824	0.927	< 0.001

CRP: C-reactive protein

Table 6. Cut-off values for uric acid in predicting coronary ectasia

	95% Confidence Interval			p
	Area Under the Curve	Minimum	Maximum	
Uric Acid	0.991	0.973	1.000	< 0.001
Uric Acid <5.5 / 5.5 ≤	0.945	0.908	0.982	< 0.001
Uric Acid <6.0 / 6.0 ≤	0.995	0.984	1.000	< 0.001
Uric Acid <6.5 / 6.5 ≤	0.931	0.892	0.970	< 0.001

to the controls. This data suggests that the underlying inflammatory condition has an important role in CAE as in CAD.

In conclusion, we observed significantly higher levels of SUA and CRP in CAE patients compared to the normal population, but no significant difference was found compared to CAD patients. These results show that both CAE and CAD shared common pathophysiological mechanisms. Further studies with larger population are needed to clarify the clear roles of these markers in common pathophysiological mechanisms.

Limitations

This study has some limitations; first, the retrospective design limited our study. Second, we did not perform an analysis to assess the prognostic value of CRP and SUA in CAE. The pathogenesis of CAE and CAD is similar and most of the conducted studies in stable CAD have shown the prognostic value of these indices⁽²⁴⁾. From this point we thought that there can be a prognostic value of these indices in CAE patients. For filling the literature gap of this topic, prospective randomized controlled studies should be done. Third, angiography cannot evaluate the plaque burden, patients without evidence of luminal narrowing by angiography may also have plaque burden in the wall of the coronary vessels. It would be better to analyse with intravascular techniques such as ultrasound whether isolated CAE patients had evidence of atherosclerotic plaque. Fourth, although the formation of CAE is a slow and chronic condition, we just evaluated a single serum CRP and SUA levels in this study.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

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