The relationship between serum endocan levels and the presence/severity of isolated coronary artery ectasia

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Objective The aim of this study was to investigate the relationship between serum endocan levels and the presence and severity of isolated coronary artery ectasia (CAE).

Patients and methods A total of 52 patients with CAE without obstructive coronary artery disease and 33 participants with a normal coronary artery were included in this study. The severity of CAE was graded according to Markis classification. Serum endocan levels were measured by enzyme-linked immunosorbent assay method.

Results In multivariate regression analysis, high sensitivity C-reactive protein and endocan levels were found to be significantly associated with the presence of isolated CAE. However, there was no relationship between serum endocan levels and the severity of CAE according to Markis classification.

Conclusion Plasma endocan levels may reflect the presence of isolated CAE, suggesting that endocan may be involved in the pathogenesis of isolated CAE. *Cardiovasc Endocrinol Metab* 7:42–46 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Coronary artery ectasia (CAE), commonly known as dilatation more than 1.5 times the normal vessel diameter, is a common disease observed during coronary angiography [1]. The incidence of CAE is in the range of 1–5% in angiographic examinations [2]. The isolated form of CAE, which has been defined as CAE without important coronary artery stenosis, constitutes a small portion of the total CAE cases with a rate of 0.1–0.8% [3]. The etiopathogenesis of CAE is not clearly understood yet. Besides congenital, inflammatory, and connective tissue disorders, atherosclerotic lesions may be a potential cause for the development of CAE, because they are often associated with coronary artery disease (CAD) [4]. CAE is an independent predictor of mortality, and the mortality rate of patients with a coronary aneurysm but without obstructive disease is similar to those with multivessel disease [5,6]. This mortality increase could be explained by myocardial ischemia and/or infarction caused by inadequate dilatation of coronary arteries and the decrease in coronary flow velocity caused by endothelial dysfunction, turbulence, and thrombosis in ectatic vessel segments [7,8].

Endocan, also known as endothelial cell-specific molecule 1, is a soluble 50 kDa proteoglycan, constituting a mature polypeptide of 165 amino acids and a single dermatan sulfate chain covalently linked to the serine

residue at position 137 [9]. Endocan is synthesized and secreted by the activated vascular endothelial cells [10]. Endocan plays a major role in the pathophysiology of endothelial dysfunction by regulating physiological or pathological processes [11,12]. Previous studies have shown that increased endocan levels in patients with subclinical or severe atherosclerosis were associated with endothelial activation and dysfunction [13,14].

According to these findings, we hypothesized that there might be a relationship between endocan levels and isolated CAE.

Patients and methods

This cross-sectional study was approved by the local ethical committee of Ankara Numune Education and Research Hospital and informed consents were obtained from all patients before involving them in the study.

Study population

This study included patients who were referred to the cardiology outpatient clinic for stable angina pectoris with positive exercise test or myocardial perfusion scintigraphy and who underwent coronary angiography between July 2015 and June 2016. A total of 150 patients were planned to be included in the study. Sixty-five patients were excluded and we continued to work with 85 patients. A total of 52 patients were included in the

isolated CAE group. Thirty-three individuals in the same age group constituted the normal coronary artery (NCA) group. Our exclusion criteria were acute or chronic infections, inflammatory diseases, heart failure (ejection fraction <40%), atrial fibrillation, anemia, chronic renal failure (serum creatinine >2.0 mg/dl), liver cirrhosis, malignancy, severe heart valve disease, acute coronary syndromes (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina pectoris), previous percutaneous coronary intervention, coronary artery bypass grafting, and obstructive CAD.

Arterial hypertension was diagnosed in patients with a blood pressure higher than 140/90 mmHg on at least two measurements or in patients using antihypertensive drugs. Diabetes mellitus was identified as recurrent measurements of fasting blood sugar higher than 126 mg/dl or as anti-diabetic drug use. Hypercholesterolemia was considered as total serum cholesterol more than 200 mg/dl or as the use of lipid-lowering medication. Transthoracic echocardiography was performed in all patients in the study. Left ventricular ejection fraction was calculated by Simpson's technique.

Coronary angiography and Markis classification

We used Judkins technique for coronary angiography in all patients. After obtaining images by standard approaches, each angiogram was interpreted by two independent cardiologists. A third cardiologist was consulted when they fell into disagreement. According to the angiographic definition used in this study, a vessel was considered to be ectatic when its diameter was at least 1.5 times that of the adjacent normal segment in segmental ectasia. The severity of isolated CAE was determined according to the Markis classification [6]. In decreasing order of severity, type I defines diffuse ectasia of two or three vessels, type II defines diffuse disease in one vessel and localized disease in another vessel, type III defines diffuse ectasia of one vessel only; type IV defines localized or segmental ectasia. Obstructive CAD was described as stenosis of more than 50% of the diameter at one or more major epicardial arteries.

Measurements

All blood samples were taken from the peripheral venous blood in the catheter laboratory after coronary angiography. The samples were centrifuged at 4000g for 10 min, and then the serum was stored at -80°C until the measurement of endocan levels. Serum lipid parameters, creatinine levels, hemogram parameters, high sensitivity C-reactive protein (hsCRP) levels were measured using local laboratory instruments. Endocan levels were determined using a commercially available sandwich enzyme-linked immunosorbent assay kit with high sensitivity and specificity for the detection of human endocan (Boster, Wuhan, China). All serum samples were analyzed by enzyme-linked immunosorbent assay in duplicate, and the results were averaged. The intratest

and inter-range coefficients of variation were calculated as 4.3 and 4.7%, respectively.

Statistical analysis

In all statistical analysis, SPSS 22.0 statistical package program for Windows (SPSS Inc., Chicago, Illinois, USA) was used. The Kolmogorov-Smirnov test was used to assess the distribution pattern. Normally distributed continuous variables were presented as mean $\pm$ SD, and those without a normal distribution were presented as median and interquartile range. Categorical variables were presented as number and percentage. The Student *t*-test was used to compare parametric continuous variables and the Mann-Whitney *U*-test was used to compare nonparametric continuous variables. Comparisons of multiple groups were carried out by the Kruskal-Wallis tests or analysis of variance, as appropriate. The χ^2 -test was used to compare the categorical variables. Logistic regression analysis was performed to find independent predictors of isolated CAE. Variables that had an unadjusted *P* value of less than 0.15 in logistic regression analysis were identified as potential risk markers and then included in the full model. We eliminated potential risk markers by likelihood ratio tests with reduced model using multivariate logistic regression analysis. A *P* value of less than 0.05 was considered statistically significant with a confidence interval of 95%. The receiver operating characteristic curve was used to show the sensitivity and specificity of endocan levels and to calculate the optimal cutoff value for predicting the presence of isolated CAE.

Results

A total of 85 patients were included in the study. Of these 85 patients, 52 were in the isolated CAE group, and 33 were in the NCA group. The clinical, laboratory, and angiographic data of the patients are shown in Table 1. Hemoglobin level, and lymphocyte and platelet counts were significantly higher in the NCA group. However, hypertension, hsCRP, and endocan levels were significantly higher in the isolated CAE group. Figure 1 depicts endocan concentrations in the isolated CAE group and the NCA group. The endocan levels were significantly higher in patients in the isolated CAE group compared with those in the NCA group ($P < 0.001$). In contrast, as seen in Fig. 2, there was no statistically significant difference between subsets of CAE patients according to Markis classification with regard to endocan levels ($P > 0.05$). Multivariate regression analysis showed that hsCRP and endocan levels were independent predictors of the presence of isolated CAE (Table 2).

Finally, receiver operating characteristic curve analysis was used to determine predictive value endocan in isolated CAE. The optimal cutoff value for endocan was calculated as 3.2 ng/ml. The area under the curve was 0.860. At this cutoff value, the sensitivity and specificity of endocan were 79 and 76%, respectively. We also

Table 1 Clinical, laboratory, and angiographic characteristics of the study population

Variables	Control (n = 33)	Isolated CAE (n = 52)	P value
Male [n (%)]	25 (75.7)	40 (76.9)	0.450
Age (mean ± SD)	56 ± 10	58 ± 10	0.754
Diabetes mellitus [n (%)]	6 (18.2)	14 (26.9)	0.360
Current smoker [n (%)]	10 (30.3)	11 (21.2)	0.195
Hypertension [n (%)]	6 (18.2)	22 (42.3)	0.015*
White blood cell count (mean ± SD) ($\times 10^9/l$)	7.75 ± 1.34	8.21 ± 1.78	0.213
Hemoglobin (mean ± SD) (g/l)	14.55 ± 1.20	13.79 ± 1.55	0.019*
Neutrophil count (mean ± SD) ($\times 10^9/l$)	4.96 ± 1.48	5.21 ± 1.48	0.455
Lymphocyte count (mean ± SD) ($\times 10^9/l$)	4.58 ± 1.53	2.09 ± 0.75	<0.001*
Platelet count (mean ± SD) ($\times 10^9/l$)	276 ± 73	230 ± 63	0.003*
Triglyceride [median (IQR)] ($\mu\text{mol/l}$)	1.53 (1.19–1.75)	1.38 (1.13–1.99)	0.278
Total cholesterol (mean ± SD) ($\mu\text{mol/l}$)	4.01 ± 0.65	4.74 ± 0.98	0.145
Low-density lipoprotein (mean ± SD) ($\mu\text{mol/l}$)	2.67 ± 0.67	2.95 ± 0.83	0.785
High-density lipoprotein (mean ± SD) ($\mu\text{mol/l}$)	1.17 ± 0.26	1.09 ± 0.23	0.239
Creatinine (mean ± SD) ($\mu\text{mol/l}$)	64.8 ± 17.5	70.9 ± 16.0	0.135
Left ventricular ejection fraction (mean ± SD) (%)	61 ± 4	60 ± 5	0.258
High sensitivity C-reactive protein [median (IQR)] (nmol/l)	66.6 (19.0–238.1)	190.4 (123.8–533.3)	<0.001*
Endocan (mean ± SD) (ng/dl)	2.64 ± 1.26	5.25 ± 2.22	<0.001*
Systolic blood pressure (mean ± SD) (mmHg)	132 ± 12	131 ± 13	0.370
Diastolic blood pressure (mean ± SD) (mmHg)	75 ± 12	75 ± 16	0.450
Markis classification [n (%)]			
Type I	–	10 (19.2)	–
Type II	–	12 (23.1)	–
Type III	–	9 (17.3)	–
Type IV	–	21 (40.3)	–

CAE, coronary artery ectasia; IQR, interquartile range.

*Statistically significant.

Fig. 1

The graph shows the relationship between normal coronary artery (NCA) and coronary artery ectasia (CAE) groups of endocan.

Fig. 2

The graph shows the relationship of endocan level with subgroups of Markis classification.

measured the power analysis, and we found that our result was 1, which provides a strong power (Fig. 3).

Discussion

In this study, we found a statistically significant relationship between high endocan levels and isolated CAE. To the best of our knowledge, this is a study that evaluated endocan levels as a novel marker for inflammatory and endothelial dysfunction in patients with isolated CAE and then compared the results with those obtained in patients with NCAs.

With the increase in the number of patients undergoing coronary angiography, we identify CAE in more patients. CAE is an independent predictor of mortality, and, in some studies, the mortality rate of patients with nonobstructive coronary artery aneurysms is similar to that of patients with multivessel disease [5,6]. In a large cohort study on CAE, the 5-year mortality in patients with coronary artery aneurysm was reported as 26% in 1983 [6]. In contrast, two recent studies found significantly lower mortality rates in CAE

Table 2 Multiple logistic regression analysis showing independent predictors of isolated coronary artery ectasia

Variables	P value	Adjusted OR (95% CI)
Endocan	< 0.001*	1.025 (1.016–1.035)
Hemoglobin	0.708	0.875 (0.550–1.100)
Hypertension	0.391	1.160 (0.985–1.330)
Lymphocyte	0.105	1.090 (0.980–1.200)
Platelet	0.210	1.155 (0.895–1.365)
High sensitivity C-reactive protein	0.001*	1.040 (1.005–1.075)

CI, confidence interval; OR, odds ratio.

*Statistically significant.

Fig. 3

The graph shows the receiver operating characteristic (ROC) curve of endocan level for prediction of coronary artery ectasia. AUC, area under the curve.

patients. In the first study, the cardiovascular mortality rate was 2% after a mean follow-up of 49 ± 21 months in 258 patients with CAE [15]. The second study, which included 540 patients with CAE, reported 2.22% mortality after 36 months of follow-up [16]. The decrease in mortality over time may be attributable to better management of CAE and the improvements in medicine. The pathophysiological mechanism of CAE has also become an important research topic because of high mortality rate. Although the etiology and pathophysiology of CAE are still unclear, some pathological mechanisms have been proposed. CAE is considered to be a large positive remodeling of the atherosclerotic coronary artery [17]. The most emphasized mechanisms of this remodeling are the enzymatic degradation of the extracellular matrix and the thinning of the tunica media layer of the vessel caused by severe chronic inflammation [18]. Markis *et al.* [7] examined ectatic layers by postmortem histopathological examination and suggested the destruction of vascular media layer in ectasia. Moreover, more than half of the CAE patients have CAD. However, excessive release of interstitial nitric oxide (NO) is suggested as another aspect of this pathology. Inflammatory cells are important factors in the production

of NO by inducible NO synthase. Chronic exposure to NO may cause hyaline degeneration in the intima and media layers of the coronary arteries and may lead to abnormal coronary dilatation [19]. In a recent study, plasma levels of vascular endothelial growth factor (VEGF) in isolated CAE patients were investigated, and a new insight into the molecular mechanisms of the widely isolated CAE was presented. Plasma levels of VEGF, matrix metalloproteinase-2 (MMP-2), tissue inhibitors of matrix metalloproteinase-1 (TIMP-1) and tissue inhibitors of MMP-2 (TIMP-2), as well as C-reactive protein (CRP), were investigated in a study [20]. As a result of this study, VEGF levels in patients with diffuse isolated CAE were higher than those in patients with NCAs or obstructive CAD. MMP-2 and TIMP-1 levels were similar in these three groups, but TIMP-2 levels were lower in patients with diffuse isolated CAE than the other two groups. Although these studies had smaller samples sizes, more severe and extensive chronic inflammation in the coronary circulation in CAE patients suggests that a greater amount of vascular wall inflammation may have a role. hsCRP levels, a marker of systemic inflammation, are present in all atherosclerotic diseases and are associated with poor prognosis. Previous studies have shown that hsCRP levels are elevated in patients with CAE, which is seen as a derivative of atherosclerotic disease [16,21]. CRP may cause endothelial dysfunction and medial breakdown by increasing monocyte adhesion to endothelial cells and secretion of MMPs [22]. The prothrombotic effects of CRP were shown in humans [23] and transgenic mice. High hsCRP levels that were observed in our study support these data.

Endocan is a soluble proteoglycan secreted by human vascular endothelial cells, especially by inflamed endothelium [9]. Initial studies have shown that endocan is oversynthesized in a variety of diseases such as sepsis, cancer, obesity or inflammatory diseases [24]. It is demonstrated that endocan plays an important role in endothelial dysfunction, as it regulates cell adhesion in inflammatory disorders [25]. VEGF is a potent proangiogenic factor, and it upregulates endocan expression [26]. Roudnicky *et al.* [27] have investigated patients with bladder cancer and reported that endocan was strongly upregulated on tumor vascular endothelium and that its expression correlated with the invasiveness of bladder cancer. High endocan levels have been shown in some diseases such as hypertension, coronary slow flow phenomenon, and Behcet's disease where endothelial dysfunction is present in the etiology [28–30]. Elevated endocan levels have been associated with carotid intima-media thickness in patients at increased risk for atherosclerotic diseases, such as those with polycystic ovary syndrome [31]. Endothelial dysfunction is considered to be the primary pathology in various stages of the formation of atherosclerosis, including early development of atheroma and atherosclerotic plaque imbalance [32,33]. Endocan is an important marker of subclinical

atherosclerosis [34] and is useful to investigate the role of CAE in the etiopathogenesis.

According to these findings and the pathophysiological role of inflammation in isolated CAE, we hypothesized that endocan might be associated with isolated CAE. Our results showed that endocan might have a role in the development of CAE. Endocan was significantly high in patients with CAE, but there was no difference between subsets of patients according to Markis classification with regard to endocan levels. Thus, there is an inflammatory status in patients with CAE, but there might also be some additional factors affecting the severity or extent of CAE. Another finding of our study is that there was a positive correlation between hsCRP levels and endocan levels, which also supports the role of systemic inflammation in our study. Finally, our findings indicated that an endocan level higher than 3.2 ng/ml was significantly associated with the presence of isolated CAE.

Limitations

This study has several limitations. First, our research did not include a histopathological examination of obstructive CAD or ectatic segments. We have a relatively small number of patients, and further studies with larger sample sizes are warranted. Finally, further tests such as intravascular ultrasonography could not be used in the diagnosis of our control group; hence, the diagnosis of normal CAD was observational.

Conclusion

We concluded that endocan is a significant predictor of the presence of CAE and hsCRP, a systemic inflammatory response, and is higher in CAE patients. Therefore, endocan may be valuable in helping uncover the underlying pathogenesis of CAE. Larger prospective studies are needed to confirm the role of endocan in isolated CAE.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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