

Association of serum prolidase activity in patients with isolated coronary artery ectasia

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ABSTRACT

Objective: Coronary artery ectasia (CAE) is defined as an angiographic enlargement of a portion of the coronary artery between 1.5 and 2 times the diameter of the adjacent normal coronary artery. It has been demonstrated that increased serum prolidase activity (SPA) is associated with increased collagen turnover. We aimed to analyze the relationship between CAE and serum SPA levels.

Methods: This study used a prospective case protocol design. A total of 40 consecutive patients with isolated right CAE and normal coronary arteries (23 men, 17 women; mean age, 62.4±10.8 years) were evaluated. The control group included the same number of consecutive patients with angiographically normal coronary arteries (20 men, 20 women; mean age, 63.8±11.1 years). Clinical characteristics, laboratory results, cardiovascular risk factors, and medication use were recorded. SPA was measured using a spectrophotometer. Student's t-test, Mann-Whitney U test, chi-square test, Pearson's and Spearman's correlations, logistic regression analysis, and ROC curve analysis were used for statistical analysis.

Results: SPA was significantly higher in the CAE group compared with the control group (1635.2±492.0 U/L and 986.2±422.3 U/L, respectively; $p<0.001$). The relationship of SPA with CAE proved to be significant ($r=0.512$; $p<0.001$). SPA also served as an independent predictor of CAE (OR=1.003; 95% CI, 1.001–1.005; $p=0.002$). The SPA value of 1170 U/L was predictive of CAE, with a sensitivity of 85% and specificity of 60% (AUC=0.854; 95% CI, 0.763–0.944; $p<0.001$).

Conclusion: The activity of this enzyme was significantly correlated with CAE. (*Anatol J Cardiol* 2018; 19: 110-6)

Keywords: coronary artery ectasia, collagen turnover, serum prolidase activity

Introduction

Coronary artery ectasia (CAE) is defined as an angiographic enlargement of a portion of the coronary artery between 1.5 and 2 times the diameter of the adjacent normal coronary artery. Coronary aneurysms were defined as those with luminal dilatation of >2.0-fold of normal limits (1). Angiographic frequency of CAE has been reported to be 0.3%–5.3% in various series (2, 3). The etiopathogenesis of this clinical entity is not fully understood. The most common cause of CAE in the Western population is atherosclerotic coronary artery disease (CAD). Congenital anomalies are the second most common etiologic cause. Kawasaki disease, congenital anomalies, collagen tissue diseases, and connective tissue diseases are other common causes of CAE. Percutaneous coronary invasive procedures and trauma rarely lead to CAE (4, 5). Chest pain is seen as the primary symptom of CAE. However, dysrhythmias, acute coronary syndromes, and sudden cardiac death are other clinical conditions that are observed in CAE (6, 7).

Collagen is one of the main proteins of the extracellular

matrix (ECM). Increase in ECM turnover may play a role in the pathophysiology of atherosclerosis progression and endothelial dysfunction (8, 9). One of the enzymes in collagen biosynthesis is prolidase. Prolidase (manganese-dependent) is an iminodipeptidase and is responsible for the degradation of dipeptides with C-terminal proline and hydroxyproline. It plays a role in collagen re-synthesis and cell growth. Prolidase enzyme is present in many tissues, such as intestinal mucosa; tissues of the kidney, liver, brain, heart, uterus, and thymus; erythrocytes; leukocytes; fibroblasts; and plasma. Increase in enzyme activity is closely related to collagen degradation (10-12). Many recent studies have highlighted the relationship between cardiovascular diseases and serum prolidase activity (SPA). The prevalence of CAD, atrial fibrillation in patients with mitral stenosis, and hypertension (HT) has been shown to be correlated with SPA (13, 14).

Patients with CAE are frequently encountered in coronary angiography laboratories. Prolidase is an important enzyme in atherosclerosis and endothelial dysfunction. This study investigated the level of prolidase in patients with CAE.

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Clinical significance

SPA might be an indicator of vascular intimal ECM collagen turnover and plays a role in the development of atherosclerotic plaques, vascular remodeling, and plaque ruptures, causing acute coronary syndrome.

Our study demonstrates higher SPA levels in CAE patients and focuses on the relationship between CAE and high SPA levels. Our results also indicate that increased SPA was an independent predictor for CAE. This increase in levels may support the hypothesis that the high levels may be related to the development of CAE.

Methods

Study population

This was a prospective case-control study that was performed in Adiyaman University Training and Research Hospital and was institutionally approved by the Ethics Committee. All participants signed an informed consent form to participate in the study, which lasted for 1 year starting in January 2016. The study included patients with suspected coronary ischemia after positive or equivocal results of noninvasive ischemic tests and who experienced typical chest pain. All patients underwent coronary angiography. The study population included 40 consecutive patients with isolated right CAE and normal coronary arteries (23 men, 17 women; mean age, 62.4 ± 10.8 years). The control group included the same number of consecutive patients with angiographically normal coronary arteries and without CAE (20 men, 20 women; mean age, 63.8 ± 11.1 years). Among the 89 patients, two were excluded because of a history of myocardial infarction and left ventricular dysfunction, three were excluded because of left ventricular hypertrophy and heart valve disease, and one was excluded because of HT and renal failure. Furthermore, three patients were excluded because of other reasons, such as cerebrovascular disease ($n=1$), hepatic dysfunction and autoimmune disease ($n=1$), and neoplastic disease and osteoporosis ($n=1$). As a result, 80 patients were included in the study. Antioxidants or drugs acting on the collagen cycle (angiotensin receptor blocker or angiotensin-converting enzyme inhibitor, beta blockers, acetylsalicylic acid, and statins) were stopped 3 weeks before the start of the study. HT was defined as having a mean systolic blood pressure (SBP) of >140 mmHg and/or diastolic blood pressure (DBP) of >90 mmHg or ongoing antihypertensive drug usage. Diabetes mellitus (DM) was defined as fasting blood sugar level of ≥ 126 mg/dL or ongoing antidiabetic drug usage. Hyperlipidemia (HL) was defined as total cholesterol level of >200 mg/dL, dyslipidemia history, and/or undergoing anti-lipidemic therapy. Existing cigarette smoking was defined as >10 cigarettes per day. Body mass index (BMI) was calculated using the standard formula of weight (kg)/height squared (m^2). The left ventricular ejection fraction (LVEF) was automatically calculated according to the modified Simpson's method using the software on the echocardiography device (15).

Prolidase assay

From all patients, 5 mL of blood was collected in vacutainer tubes. Blood samples were stored for 30 min at room temperature and then centrifuged at 3000 rpm for 10 min in a Hettich centrifuge device. Prolidase enzyme levels were maintained for analysis by storing blood serum at -80°C . When the study was performed, all serum samples were brought to room temperature, the serum was resolved, and the prolidase enzyme levels were manually examined in the biochemistry laboratory using the modified Chinard method.

The prolidase enzyme was assayed 40 times by dilution with serum 2.5 mmol/L Mn 2+, and trizma was buffered with HCl (pH 8.0). Preincubation was performed at 37°C for 2 h. A mixture containing glycyl-proline was incubated at 37°C for 30 min. The proline levels in the supernatants were measured using a spectrophotometer using the modified Chinard method (16). Results were expressed as U/L. The intra-assay coefficient of variation used in the current study was 3.8%.

Coronary angiography

Coronary angiography was performed via the femoral artery using the standard Judkins technique. Coronary angiography was performed on the right and left oblique planes using cranial and caudal angles at 30 fps (Allura Xper FD10, Philips Healthcare Best, The Netherlands). Coronary angiography images of the patients were evaluated by two experienced interventional cardiologists who were blinded to the study. CAE was described by Falsetti and Carroll (17) as segmental or diffuse dilatation of coronary arteries up to 1.5 times the diameter of adjacent segments of the same artery or different arteries. This identification was used in our study. Normal segment was defined as normal coronary artery without ectasia or stenosis determined by coronary angiography. Patients with CAE with concomitant coronary stenosis were excluded from this study.

Statistical analysis

Statistical analyses were performed using IBM SPSS for Windows version 22 (SPSS Inc., Chicago, IL, USA). The normality of the data was defined using the Kolmogorov-Smirnov test. Normally distributed continuous data are shown as mean \pm standard deviation, whereas non-normally distributed data are shown as median (interquartile range). Normally distributed continuous variables were compared using the independent samples t test, and the Mann-Whitney U test was used if the distribution was skewed. Categorical data were compared using the chi-square test. Pearson is a parametric one, whereas Spearman is a non-parametric test that assessed the relationship between the two variables. Logistic regression analysis was used to determine the independent determinants of CAE. In order to predict CAE, the receiver operating characteristic (ROC) curve analysis was used to determine the SPA cutoff value. A p-value of <0.05 was considered significant.

Table 1. Baseline demographic and clinical parameters of the study population

Variables	Patients with CAE (n=40)	Control group (n=40)	P value
Age, years	62.4±10.8	63.8±11.1	0.563
Gender, male, n, (%)	23 (57.5)	20 (50.0)	0.501
DM, n, (%)	8 (20.0)	3 (7.5)	0.105
Smoking, n, (%)	36 (90.0)	4 (10.0)	<0.001*
HT, n, (%)	39 (97.5)	30 (75.0)	0.003*
HL, n, (%)	20 (50)	7 (17.5)	0.002*
COPD, n, (%)	10 (25.0)	6 (15.0)	0.264
Family history, n, (%)	15 (37.5)	5 (12.5)	0.010*
BMI (kg/m ²)	26.9±3.8 (22.4-34.2)	24.8±2.7 (20.7-33)	0.002*
LVEF (%)	52.2±5.4 (40-55)	55.2±2.9 (50-65)	0.003*
SBP (mm Hg)	116.0±15.1	102.6±8.5	<0.001*
DBP (mm Hg)	78.3±8.2	70.6±5.1	<0.001*
SPA (U/L)	1635.2±492.0	986.2±422.3	<0.001*
FPG (mg/dL)	107.1±43.8 (64-283)	136.1±43.2 (69-226)	0.043*
Creatinine, (mg/dL)	0.72±0.4	0.75±0.4	0.677
TC (mg/dL)	188.0±40.0 (120-278)	175.2±49.8 (72-278)	0.211
TG (mg/dL)	177.5±34.6 (122-256)	175.2±49.8 (78-278)	0.815
HDL (mg/dL)	33.6±10.0	40.8±10.0	0.002*
LDL (mg/dL)	133.2±35.6	107.4±26.4	<0.001*
WBC (103×µL)	10.6±3.9 (5-23)	11.4±10.2 (5-22)	0.661
HGB (g/dl)	13.8±1.9	13.2±1.7	0.217
Plt (103×µL)	236.5±76.4	246.2±76.2	0.574
Previous medications, n, (%)			
Acetylsalicylic acid	16 (40.0)	14 (35.0)	0.644
Beta blockers	8 (20.0)	7 (17.5)	0.775
ACEi/ARB	13 (32.5)	12 (30.0)	0.809
Statin therapy	6 (15.0)	4 (10.0)	0.499

*P value <0.05

BMI - body mass index, COPD - chronic obstructive pulmonary disease, DBP - diastolic blood pressure, DM - diabetes mellitus, FPG - fasting plasma glucose, HDL - high density lipoprotein, HL - hyperlipidemia, HT - hypertension, LDL - low density lipoprotein, LVEF - left ventricular ejection fraction, Plt - platelet, SBP - systolic blood pressure, SPA - serum prolidase activity, TC - total cholesterol, TG - triglyceride, WBC - white blood cell

Results

Clinical and laboratory characteristics of patients with CAE and controls are presented in Table 1. The demographic characteristics of patients in both groups, including age and gender, were similar. CAD risk factors, such as DM, was similar between the two groups ($p>0.05$), whereas, other risk factors (smoking, HT, HL, and family history) were significantly higher in the CAE group than in the control group ($p<0.001$, $p<0.001$, $p=0.002$, and $p=0.010$, respectively). The incidence of chronic obstructive pulmonary disease (COPD) was similar between the groups. The two groups were not significantly different with regard to their

therapy regimens. BMI was significantly higher in the CAE group than in the control group ($p=0.002$). In addition, SBP and DBP, fasting plasma glucose level, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels; SPA levels (Fig. 1), and LVEF were significantly different between the groups ($p<0.001$, $p<0.001$, $p=0.043$, $p<0.001$, $p=0.002$, $p<0.001$, and $p=0.003$, respectively). There were similarities in terms of other laboratory parameters.

CAE was significantly correlated with BMI, LVEF, SBP, DBP, SPA, HDL, and LDL ($r=0.284$, $p=0.011$; $r=-0.330$, $p=0.003$; $r=0.486$, $p<0.001$; $r=0.494$, $p<0.001$; $r=0.512$, $p<0.001$; $r=-0.341$, $p=0.002$; and $r=0.385$, $p<0.001$) (Table 2). LVEF was inversely correlated with SPA ($r=-0.348$, $p=0.002$) (Fig. 2). Multivariate logistic regression analysis revealed that age, smoking, HL, LVEF, SPA, HDL,

Table 2. Correlation between coronary artery ectasia and variables

Univariate Correlation Analysis		
Variables	Correlation coefficient (r)	P value
Age, years	-0.066	0.563
BMI (kg/m ²)	0.181	0.107
LVEF (%)	-0.657	<0.001*
SBP (mm Hg)	0.525	<0.001*
DBP (mm Hg)	0.344	0.002*
SPA (U/L)	0.289	0.009*
HDL (mg/dL)	-0.284	0.011*

*P value <0.05
 BMI - body mass index, DBP - diastolic blood pressure, HDL - high density lipoprotein, LDL - low density lipoprotein, LVEF - left ventricular ejection fraction, SBP - systolic blood pressure

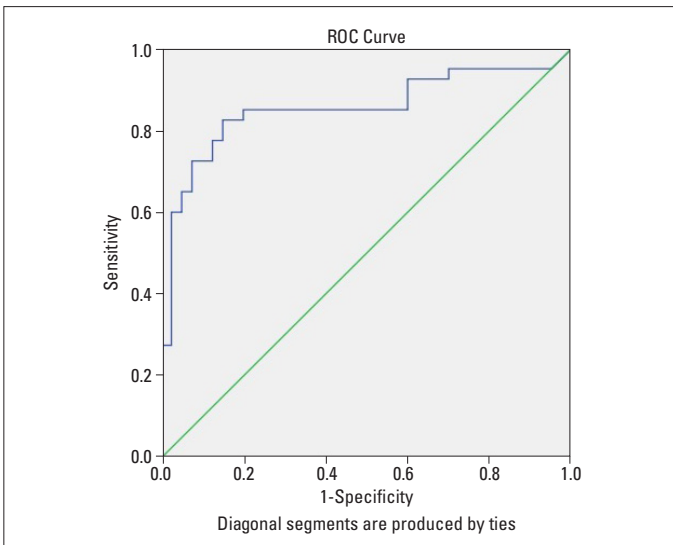


Figure 1. Serum prolidase activity levels between the groups

and LDL were independent predictors of CAE (OR=0.915, 95% CI, 0.838–1.000, $p=0.050$; OR=0.040, 95% CI, 0.006–0.254, $p=0.001$; OR=0.171, 95% CI, 0.037–0.787, $p=0.023$; OR=0.653, 95% CI, 0.431–0.990, $p=0.045$; OR=1.003, 95% CI, 1.001–1.005, $p=0.002$; OR=0.886, 95% CI, 0.808–0.972, $p=0.011$, and OR=1.036, 95% CI, 1.006–1.067, $p=0.018$, respectively; Table 3).

The SPA value of 1170 U/L was predictive of CAE, with a sensitivity of 85% and specificity of 60% (area under the curve=0.854; 95% CI, 0.763–0.944; $p<0.001$; Fig. 3).

Discussion

This study showed that SPA is significantly increased in patients with CAE compared with controls. The activity of this enzyme showed a significant and positive correlation with CAE.

It is unclear whether local or global factors play a role in the pathogenesis of CAE. It is stated that CAE is caused by the diffuse abnormality of the vascular wall, which holds many seg-

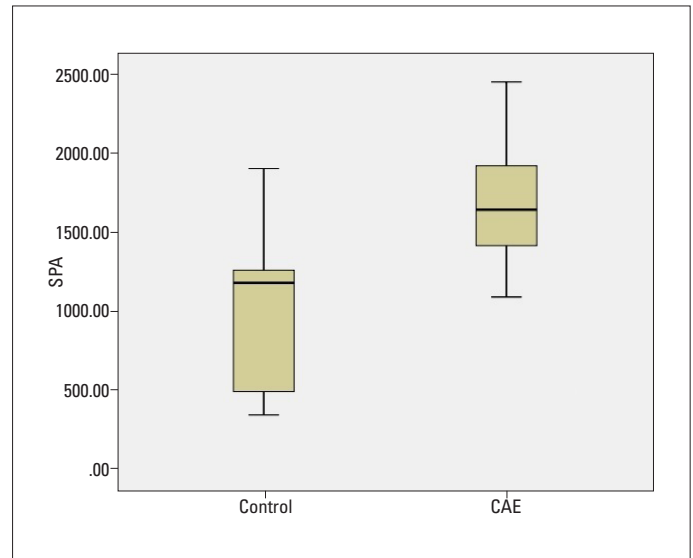


Figure 2. Correlation between serum prolidase activity and left ventricular ejection fraction

ments, and saccular ectasia form rather than fusiform ectasia represents poststenotic dilatation following stenosis (18). In our study, isolated CAE was present independently of coronary stenosis. Kajinami et al. (19) studied an autopsy of a patient with familial hypercholesterolemia and CAE who died because of acute myocardial infarction in the 19th century. Large quantities of plasma cells, macrophage, and lymphocyte infiltration were detected in the intimal and medial layers of the coronaries upon microscopic examination. Evidence of atherosclerotic reactions such as typical diffuse hyalinization, lipid deposition, intimal and medial damage, focal calcification and fibrosis, cholesterol crystals, intramural hemorrhage, and foreign body giant cell have been observed during pathological examination of CAE. Another potential factor leading to the development of CAE is nitric oxide (NO), which may cause chronic over-stimulated coronary dilatation by endothelium-derived relaxing factor. Many patients receive chronic glyceryl trinitrate therapy for angina, which may possibly worsen ectasia via NO stimulation. Another possibility is that these patients generally have CAD and atherosclerosis causes inappropriate release of NO from the endothelium (20). Quyyumi et al. (21) showed the relationship between NO and atherosclerosis and reported that coronary vascular dilatation without angiographically proven atherosclerosis was caused by increased NO because of acetylcholine.

In recent years, studies have investigated the effects of cardiac and arterial ECM turnover on plaque rupture and remodeling in atherosclerotic plaque development. ECM turnover was assessed by measuring matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) levels. Previous studies have shown that CAD is associated with enhanced turnover of ECM and collagen, which, in turn, may be associated with atherosclerotic plaque instability and vascular or ventricular remodeling. In many studies, MMP, TIMP, and subgroup levels have also been shown to be associated with acute coronary

Table 3. Independent determinants of coronary artery ectasia

Multivariate logistic regression analysis			
Variables	Odds ratio	95% CI	P value
Age, years	0.915	0.838-1.000	0.050*
Gender, male, n, (%)	0.221	0.039-1.251	0.088
DM, n, (%)	0.269	0.036-2.031	0.203
Smoking, n, (%)	0.040	0.006-0.254	0.001*
HT, n, (%)	0.222	0.045-1.091	0.064
HL, n, (%)	0.171	0.037-0.787	0.023*
Family history, n, (%)	0.535	0.108-2.638	0.442
BMI (kg/m ²)	1.324	0.991-1.770	0.058
LVEF (%)	0.653	0.431-0.990	0.045*
SBP (mm Hg)	1.043	0.950-1.145	0.376
DBP (mm Hg)	1.192	0.988-1.438	0.066
SPA (U/L)	1.003	1.001-1.005	0.002*
HDL (mg/dL)	0.886	0.808-0.972	0.011*
LDL (mg/dL)	1.036	1.006-1.067	0.018*

*P value <0.05
 BMI - body mass index, DBP - diastolic blood pressure, DM - diabetes mellitus, HDL - high density lipoprotein, HL - hyperlipidemia, HT - hypertension, LDL - low density lipoprotein, LV EF - left ventricular ejection fraction, SBP - systolic blood pressure

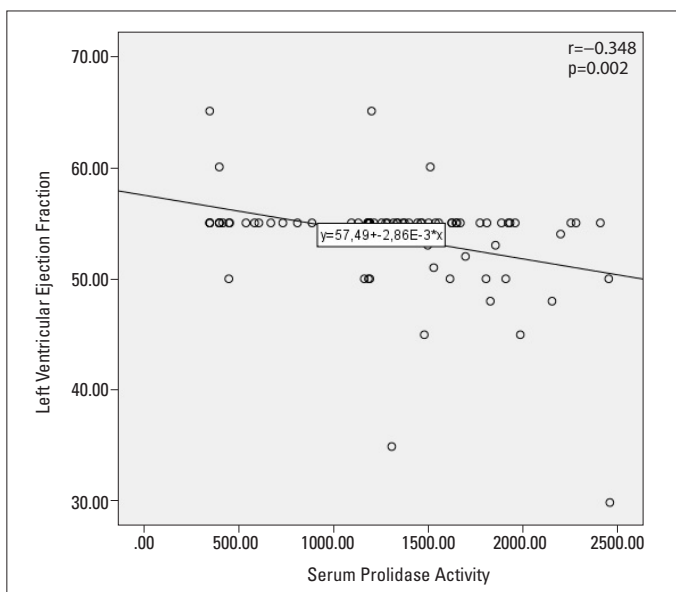


Figure 3. Receiver operating characteristic curve for the determination of the cut-off for serum prolidase activity in the prediction for coronary artery ectasia

syndromes, carotid vascular diseases, stent thrombosis, acute coronary syndromes, and severity and complexity of the lesion in CAD (22-24). In our study, MMP, TIMP, and subgroup levels were not measured.

Another marker that shows collagen and ECM turnover is the serum prolidase levels. Prolidase (manganese-dependent) consists of iminodipeptidase, C-terminal proline, and hydroxyproline. Prolidase enzyme is present in many tissues, such as intestinal

mucosa; tissue of the kidney, liver, brain, heart, uterus, and thymus; erythrocytes; leukocytes; fibroblasts; and plasma. The increase in enzyme activity is closely related to collagen degradation. The increase in enzyme level correlates with colloquine turnover (25). Demirbag et al. (13) compared healthy patients with HT and left ventricular hypertrophy to those without the disease. In this study, SPA was shown to be significantly higher in patients with HT compared with the control group and independent from the duration of HT. In another study, in 26 patients who underwent valve replacement for rheumatologic etiology, their prolidase enzyme levels were compared with 24 patients who underwent valve replacement because of degenerative etiology and 20 healthy volunteers. SPA was shown to be significantly higher in the control group than in the patient group (26).

The results of our study showed that the relationship of SPA with CAE proved to be significant. To the best of our knowledge, this study is the first to demonstrate an association between CAE and high SPA levels, and increased SPA was an independent predictor for CAE. The results of a study about the relationship between familial hypercholesterolemia and CAE showed that dyslipidemia is one of the causes of CAE (27). The serum triglyceride concentration was relatively high in this study, although none of the patients had familial hypercholesterolemia. In our study, incidence of HL and LDL levels were significantly higher in patients with CAE. In addition to this, HL, higher LDL, and lower HDL were independent predictors of CAE. There were no differences in terms of triglyceride levels in patients with CAE compared with the control patients. A recent study focused on the dependent relationship between HT and CAE (28). In our

study, the prevalence of HT was higher in patients with CAE, but HT was not an independent predictor of CAE.

Another study, which studied SPA in patients with ischemic dilated cardiomyopathy (DCM), those with idiopathic DCM, and a group of healthy controls, showed that prolidase enzyme levels in patients with ischemic DCM were significantly lower than in the other two groups. Researchers stated that the results obtained from this study were not the same as those predicted. It may be considered that lower serum prolidase levels in patients with ischemic DCM, which were normally expected to be higher in patients with ischemic etiology in other studies, may be associated with reduced collagen circulation in cardiac tissue and decreased physical activity in patients with DCM (29). In contrast with this study, in our study, reduced LVEF measures correlated with high SPA levels.

Suner et al. (30) hypothesized that SPA significantly correlates with coronary slow-flow. CAD is known to be a pathology directly associated with left ventricular diastolic dysfunction (LVDD) (31). Yildiz et al. (32) correlated the presence and prevalence of CAD with SPA using the Gensini scoring method in their study and concluded that SPA may be an independent predictive marker for coronary artery atherosclerosis. Other similar studies examining the relationship between SPA and CAD have shown that SPA is significantly associated with CAD (32). In our study, patients who had a history of CAD or prior myocardial infarction were excluded.

We think that SPA is higher in patients with CAE than in controls, and perhaps identification of CAE with higher SPA levels could identify a group at a higher risk for atherosclerosis. Literature review suggests that CAE is not a benign entity, and future studies should be performed to establish the best strategy for treatment and risk management.

Study limitations

The limitations of this study stem from an insufficient number of patients, the cross-sectional design, and a lack of long-term follow-up of patients. The absence of measurements of serum and urinary proline and hydroxyproline levels constitutes another limitation. Finally, rather than using quantitative methods such as intravascular ultrasound, visual evaluation was the only method used for diagnosis and exclusion of patients.

Conclusion

Our study suggests that SPA levels are higher in patients with CAE when compared with those with normal coronary arteries. This increase in levels may support the hypothesis that the high levels may be related to the development of CAE. The activity of this enzyme was significantly correlated with CAE.

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Peer-review: Externally peer-reviewed.

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