The association between serum angiogenin and osteopontin levels and coronary collateral circulation in patients with chronic total occlusion

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Abstract

Objective: A well-developed coronary collateral circulation lowers both in-hospital and long-term morbidity and mortality limiting the infarct. Angiogenin (AGN) and osteopontin (OPN) are known to be potent inducers of angiogenesis. The aim of the present study was to investigate the relationship between serum ANG and OPN levels and collateral filling grade in subjects with stable coronary artery disease (SCAD).
Methods: A total of 122 age- and gender-matched consecutive patients who were found to have total occlusion (n=70) and no significant stenosis in epicardial coronary arteries (n=52) who underwent coronary angiography due to SCAD between January 2015 and July 2017 were included in the study. AGN and OPN levels were measured using enzyme-linked immunosorbent assay. Coronary collateral circulation was graded using Rentrop's classification of collateral filling.
Results: A total of 52 patients (61.60±11.78 years, 61.5% male) without significant epicardial coronary artery stenosis and 70 patients (62.87±8.24 years, 65.7% male) with totally occluded coronary arteries were included in the study. Subjects with total occlusion had significantly higher levels of AGN [122.00 (79.00–623.00) pg/mL vs. 98.00 (18.00–160.00) pg/mL, p<0.001] and OPN [1863.50 (125.00–6500.00) pg/mL vs. 451.00 (112.00–1850.00) pg/mL, p<0.001] than those without significant stenosis. In addition, AGN [127.00 (87.00–623.00) pg/mL vs. 110.00 (79.00–188.00) pg/mL, p=0.011] and OPN [2681.00 (126.00–6500.00) pg/mL vs. 649.00 (125.00–4255.00) pg/mL, p=0.001] levels were significantly higher in patients with better developed collaterals. Serum AGN and OPN levels were found to be significantly associated with coronary collateral development.
Conclusion: AGN and OPN are associated with better developed coronary collateral circulation and may have therapeutic implications for the promotion of coronary collateral development. *(Anatol J Cardiol 2019; 22: 77-84)*
Keywords: coronary collateral circulation, osteopontin, angiogenin

Introduction

Ischemic heart disease (IHD) is one of the leading causes of death worldwide. A well-functioning coronary collateral circulation has been shown to have a favorable impact on mortality, myocardial infarction recurrence, and adverse cardiovascular events in patients with chronic IHD (1-3). Angiogenesis and arteriogenesis are the main mechanisms for coronary collateral development. Previous studies have shown a relationship between biomarkers related to angiogenesis and arteriogenesis and coronary collateral development (3-7).

Angiogenin (AGN) is a ribonuclease and has been shown to induce blood vessel formation (8). Transplantation of autologous mesenchymal stem cells overexpressing the AGN gene to the heart in a chronic ischemia model was associated with the improvement of heart perfusion and function (9). Previous studies have also demostrated that AGN is a marker of three-vessel coronary artery disease (CAD) (10). In addition, AGN level increases

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in acute coronary syndrome (ACS) and has a prognostic value in patients with ACS (11).

Osteopontin (OPN) is a 34 kDa, phosphorylated sialic acid-rich non-collagenous matricellular protein that functions in a variety of biological processes, including inflammation, immunity, wound repair, tumorigenesis, cell adhesion, cell migration, bone mineralization, and remodeling (12). It is a unique component of the extracellular matrix that may play an important role in the control of vascular growth. The role of OPN in ischemic limb revascularization has been demostrated in a previous study (13). In addition, decreased OPN expression has been related with impaired neovascularization, whereas overexpression of OPN has been found to be increased during angiogenesis (14).

The relationship between serum AGN and OPN levels with coronary collateral circulation in patients with stable CAD (SCAD) has not been evaluated yet in the literature. The aim of the present study was to compare AGN and OPN levels in patients who were found to have either chronic total occlusion (CTO) or no significant epicardial coronary artery stenosis during coronary angiography due to SCAD. In addition, the present study aimed to investigate the relationship between AGN and OPN levels and collateral filling grade in subjects with CTO.

Methods

This was an observational study. A total of 122 patients who were admitted to our outpatient clinics with stable angina pectoris and scheduled for elective coronary angiography between January 2015 and July 2017 were enrolled in the study. Of the 122 patients, 70 had total occlusion in at least one major coronary artery, and 52 age- and gender-matched subjects with no significant epicardial coronary artery stenosis were classified as the control group. Stable angina pectoris was diagnosed according to the American College of Cardiology/American Heart Association criteria (15). The decision of coronary angiography was made based on a positive non-invasive stress test or presence of high clinical suspicion for severe coronary artery stenosis. The study was approved by the Institutional Ethics Committee in compliance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants.

Baseline demographic and clinical characteristics including age, gender, body mass index (BMI), history of smoking, hypertension, diabetes mellitus, and family history of CAD were recorded for all patients. Diabetes mellitus was defined as plasma glucose level ≥126 mg/dL at fasting or ≥200 mg/dL at any measurement or the current use of a glucose-lowering agent. Hypertension was defined as either the current use of anti-hypertensive medication or the documentation of a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg. Family history of CAD was defined as the presence of CAD or sudden cardiac death in a first-degree relative before the age of 55 years for men and 65 years for women.

Patients with recent ACS (within the last 6 months), previous revascularization, heart failure with reduced ejection fraction (left ventricular ejection fraction <40%), sign and/or symptoms of decompensated heart failure, symptomatic peripheral vascular disease (transient ischemic attack, stroke, intermittent claudication, peripheral revascularization, or amputation), evidence of ongoing infection or inflammation, chronic kidney disease (serum creatinine >1.4 mg/dL), chronic obstructive pulmonary disease, previous diagnosis of malignancy, BMI <20 kg/m^2 or >30 kg/m^2, and patients with diabetes receiving insulin treatment were excluded from the study.

Coronary angiography

Standard Judkins technique was used for coronary artery visualization. At least two orthogonal plane images were obtained for each coronary artery. The coronary angiograms of the study population were examined again for collateral vessels by two experienced interventional cardiologists from our institute who were totally blinded to the study. CTO was defined as a complete interruption of coronary artery flow.

Coronary collateral grading was determined according to Rentrop's method (16), with grade 0, no filling of any collateral vessels; grade 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of epicardial segment; grade 2, partial filling of the epicardial artery via collateral vessels; and grade 3, complete filling of the epicardial artery via collateral vessels (17). The CTO group was divided into two groups according to the degree of collateral development. Patients who were graded as 0 or 1 were classified as the poor collateral group, whereas patients graded as 2 or 3 were classified as the better developed collateral group.

Laboratory analysis

Venous peripheral blood samples for complete blood count and biochemistry panel were withdrawn following 12 h of fasting before coronary angiography. Samples were centrifuged at 1600 rpm for 15 min and stored at −80 °C. After the completion of patient recruitment, frozen serum samples were rapidly thawed, brought to room temperature of 24 °C, and assayed for the presence of OPN (Human OPN PicoKine™ ELISA Kit; Boster, CA, USA) and AGN (Human ANG PicoKine™ ELISA Kit; Boster) by using ELISA kits according to the manufacturer's instructions. Serial dilutions of known concentrations of human OPN and AGN were used to construct a standard curve of the analytes. The intensity of the color in each well was measured on a microplate reader (Molecular Devices, SpectraMax Plus, UK). Serum OPN and AGN levels were then estimated by extrapolation from a log:log linear regression curve determined from the serially diluted OPN ranging from 5000 pg/mL to 156 pg/mL and AGN ranging from 5000 pg/mL to 78 pg/mL.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences software (IBM SPSS Statistics for

Windows, version 20.0; IBM Corp., Armonk, NY, USA). Normally distributed parameters were presented as mean ± standard deviation, and skewed parameters were expressed as median (interquartile range: minimum–maximum). Categorical variables were presented as percentage (%). Kolmogorov–Smirnov test was used to test the normality of distribution. Mann–Whitney U test or Student's t-test was used to compare continuous variables, where appropriate. Chi-square test was used to compare categorical variables. Binary logistic regression analysis was used to determine the independent associates of better developed coronary collaterals. The validity of the multiple regression model was tested by calculating the Variance Inflation Factors for the variables included in the models. A p value <0.05 was considered statistically significant.

Results

In the patient group, there were 70 patients with coronary total occlusion in at least one major coronary artery. The age of the patient group was 62.87±8.24 years. The patient group was composed of 65.7% male. In the control group, there were 52 patients with no significant epicardial coronary artery stenosis. The age of the control group was 61.60±11.78 years. The control group was composed of 61.5% male. Baseline demographic, clinical, laboratory, and echocardiographic parameters of the study population are shown in Table 1. Baseline characteristics did not differ between the two groups except high-density lipoprotein cholesterol, AGN, and OPN levels. Subjects with CTO had significantly higher levels of AGN [122.00 (79.00–623.00) vs. 98.00 (18.00–160.00) pg/mL, p<0.001] and OPN [1863.50 (125.00–6500.00) vs. 451.00 (112.00–1850.00) pg/mL, p<0.001] than the control group. Smoking and AGN and OPN levels were found to be independently associated with the presence of CTO in the multiple binary logistic regression analysis (Table 2).

When patients with CTO were grouped according to their Rentrop grade, 23 patients were classified in the poor collateral group (grades 0 and 1), and 47 patients were classified in the better developed collateral group (grades 2 and 3). Baseline characteristics were similar between these two groups except for the duration of ischemic symptoms and the number of affected coronary arteries (Table 3). Among laboratory parameters, only AGN and OPN levels differed significantly between the two groups (Table 3). AGN [127.00 (87.00–623.00) vs. 110.00 (79.00–188.00)

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

	Control group (n=52)	Chronic total occlusion group (n=70)	*P*
Clinical parameters			
Gender, male, n (%)	32 (61.5)	46 (65.7)	0.635
Age, years	61.60±11.78	62.87±8.24	0.483
BMI, kg/m^2	26.07±3.16	26.65±3.53	0.357
Smoking, n (%)	19 (36.5)	38 (54.3)	0.052
Family history of CAD, n (%)	19 (36.5)	28 (40.0)	0.698
Diabetes mellitus, n (%)	13 (25.0)	25 (35.7)	0.206
Hypertension, n (%)	32 (61.5)	47 (67.1)	0.522
Laboratory parameters			
WBC count, ×10^9/L	8.30±1.96	7.92±2.33	0.964
Fasting blood glucose, mg/dL	109.56±51.30	121±43.19	0.184
Total cholesterol, mg/dL	201.96±45.42	190.05±46.05	0.158
LDL cholesterol, mg/dL	125.88±33.58	119.06±38.53	0.309
HDL cholesterol, mg/dL	44.50±12.16	39.16±7.22	0.003
Triglyceride, mg/dL	157.86±70.95	159.17±80.00	0.926
Angiogenin, pg/mL	98.00 (18.00-160.00)	122.00 (79.00-623.00)	<0.001*
Osteopontin, pg/mL	451.00 (112.00-1850.00)	1863.50 (125.00-6500.00)	<0.001*
Echocardiographic parameters			
LV end-diastolic diameter, mm	4.84±0.63	4.94±0.50	0.337
LVEF, %	60.57±4.52	59.25±8.04	0.290

*P<0.0, statistically significant
BMI - body mass index; CAD - coronary artery disease; HDL - high-density lipoprotein; LDL - low-density lipoprotein; LV - left ventricular; LVEF - left ventricular ejection fraction; WBC - white blood cell

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Table 2. Binary logistic regression analyses to determine the independent associates of chronic total occlusion

Variables	Univariate		Multiple	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Smoking	2.062 (0.989-4.300)	0.053	3.994 (1.012-15.765)	0.048*
Fasting blood glucose, mg/dL	1.006 (0.997-1.014)	0.189	-	-
Total cholesterol, mg/dL	0.994 (0.986-1.002)	0.158	-	-
HDL cholesterol, mg/dL	0.944 (0.906-0.983)	0.005*	-	-
Angiogenin, pg/mL	1.026 (1012-1.040)	<0.001*	1.046 (1.016-1.077)	0.002*
Osteopontin, pg/mL	1.002 (1.001-1.003)	<0.001*	1.002 (1.001-1.003)	0.007*

*$P<0.05$, statistically significant
CI - confidence interval; HDL - high-density lipoprotein; OR - odds ratio

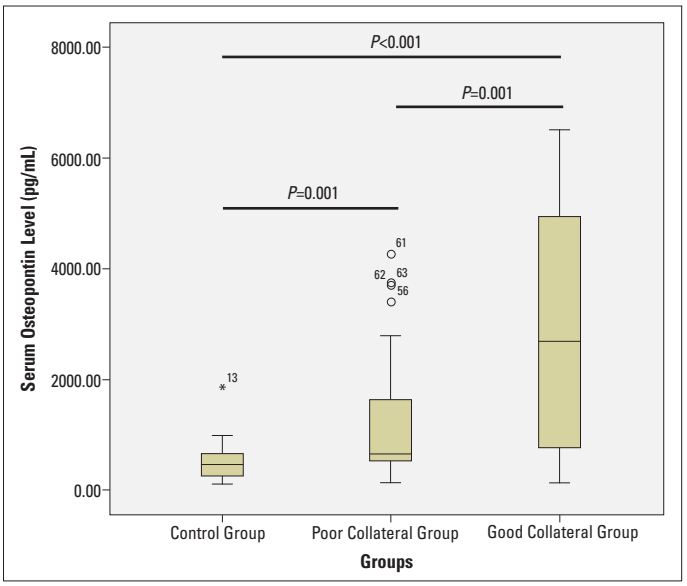


Figure 1. Box plot graph depicting osteopontin levels in the control, poor, and good coronary collateral groups

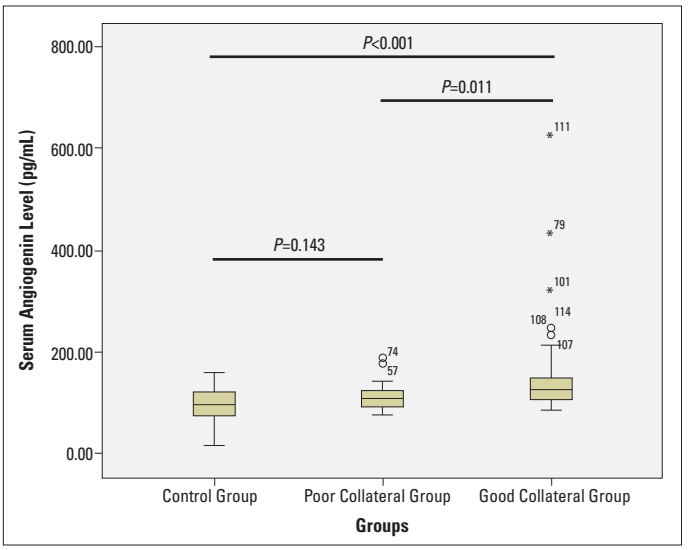


Figure 2. Box plot graph depicting angiogenin levels in the control, poor, and good coronary collateral groups

pg/mL, p=0.011] and OPN [2681.00 (126.00–6500.00) vs. 649.00 (125.00–4255.00) pg/mL, p=0.001] levels were significantly higher in patients with better developed coronary collaterals than in those with poor collateral circulation. Box plot graphs depicting OPN and AGN levels in the control, poor, and good coronary collateral groups, including p values, are shown in Figures 1 and 2.

The multiple binary logistic regression analysis revealed that AGN [odds ratio (OR) 1.032; 95% confidence interval (CI) 1.008–1.057, p=0.010] and OPN (OR 1.001; 95% CI 1.000–1.001, p<0.001) levels were independently associated with better developed coronary collateral circulation in patients with CTO (Table 4).

Discussion

The present study demonstrated an association between serum AGN and OPN levels and the presence of coronary CTO. In addition, serum AGN and OPN levels were found to be significantly associated with better coronary collateral circulation. To the best of our knowledge, this is the first study demonstrating the relationship between AGN and OPN levels and the presence of coronary CTO and degree of coronary collateral development.

AGN is a potent angiogenic growth factor related to endothelial cell proliferation. It was first isolated as a tumor angiogenic factor based on its angiogenic activity; therefore, subsequent studies have focused mainly on its angiogenic capacity (18). It has been shown to interact with all steps of angiogenesis, including migration, proliferation, and tube formation (19). Previous studies have suggested that AGN also plays a role in regulating rRNA transcription in various conditions, such as cancer, chronic heart failure, ACS, wound healing, and asthma (11, 20-23).

Tello-Montoliu et al. (11) have demonstrated that plasma AGN levels are signiŞcantly increased in ACS, and that high AGN levels are predictive of adverse events during follow-up. AGN-modified mesenchymal stem cells (MSCs) have been shown to

Table 3. Baseline demographic and clinical parameters of the study population regarding Rentrop's classification of coronary collateral filling

	Poor collateral (n=23)	Better developed collateral (n=47)	*P*
Clinical parameters			
Gender, male, n (%)	15 (65.2)	31 (66.0)	0.951
Age, years	63.30±7.85	62.66±8.5	0.761
BMI, kg/m^2	26.66±2.91	26.65±3.82	0.996
Smoking, n (%)	14 (60.9)	24 (51.1)	0.439
Family history of CAD, n (%)	10 (43.5)	18 (38.3)	0.678
Diabetes mellitus, n (%)	6 (26.1)	19 (40.4)	0.240
Hypertension, n (%)	16 (69.6)	31 (66.0)	0.763
Gensini score	32 (2-32)	32 (4-32)	0.193
Duration of angina pectoris, months	3 (3-72)	25 (3-350)	0.001*
No. of coronary arteries with severe stenosis, n (%)			
1	13 (56.5)	40 (85.1)	0.022*
2	9 (39.1)	7 (14.9)	
3	1 (4.3)	0 (0.0)	
Medications			
Renin–angiotensin system blockers, n (%)	14 (60.9)	28 (59.6)	0.917
Beta blockers, n (%)	16 (69.6)	28 (59.6)	0.416
Calcium channel blockers, n (%)	2 (8.7)	7 (14.9)	0.467
Statins, n (%)	16 (69.6)	26 (55.3)	0.253
ASA, n (%)	19 (82.6)	34 (72.3)	0.347
Glucose-lowering drugs, n (%)	3 (13)	13 (27.7)	0.171
Laboratory parameters			
WBC count, ×10^9/L	8.21±2.69	7.78±2.15	0.473
Fasting blood glucose, mg/dL	113.13±43.30	124.85±43.08	0.290
Total cholesterol, mg/dL	185.35±48.28	192.35±45.27	0.554
LDL cholesterol, mg/dL	114.65±39.24	121.21±38.41	0.507
HDL cholesterol, mg/dL	38.48±8.97	39.49±6.28	0.586
Triglyceride, mg/dL	161.09±105.89	158.23±65.08	0.890
Angiogenin, pg/mL	110.00 (79.00-188.00)	127.00 (87.00-623.00)	0.011*
Osteopontin, pg/mL	649.00 (125.00-4255.00)	2681 (126.00-6500.00)	0.001*
Echocardiographic parameters			
LV end-diastolic diameter, mm	5.0±0.64	4.9±0.42	0.458
LVEF, %	59.87±4.83	58.95±9.25	0.656

*P<0.05, statistically significant
ASA - acetylsalicylic acid; BMI - body mass index; CAD - coronary artery disease; HDL - high-density lipoprotein; LDL - low-density lipoprotein; LV - left ventricular; LVEF - left ventricular ejection fraction; WBC - white blood cell

enhance the tolerance of engrafted MSCs to hypoxia injury in vitro and improve their viability in infarcted hearts, thus helping to preserve the left ventricular (LV) contractile function and attenuate LV remodeling through vasculogenesis (19). Krecki et al. (10) have reported that AGN is a novel marker of three-vessel CAD, showing a relationship with the angiographic severity of the disease. In our study, AGN levels were higher in patients with coronary CTO and were independently associated with better developed coronary collateral circulation.

OPN is a transformation-related phosphorylated acidic glycoprotein (12). It is a key player in essential biological phenomena, such as inflammation, autoimmune disease progression,

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Table 4. Binary logistic regression analyses to determine the independent associates of better developed coronary collateral circulation

Variables	Univariate		Multiple	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Gensini score	1.054 (0.969-1.147)	0.222	-	-
Duration of angina pectoris, months	1.018 (1.00-1.036)	0.051	1.023 (1.00-1.047)	0.052
No. of coronary arteries with severe stenosis, n	0.232 (0.077-0.700)	0.009*	-	-
Glucose-lowering drugs, n	0.392 (0.100-1.546)	0.181	-	-
Angiogenin, pg/mL	1.018 (1.00-1.037)	0.046*	1.032 (1.008-1.057)	0.010*
Osteopontin, pg/mL	1.001 (1.00-1.001)	0.002*	1.001 (1.000-1.001)	<0.001*

*$P<0.05$, statistically significant
CI - confidence interval; OR - odds ratio

bone remodeling, angiogenesis, aortic stenosis, and tumor cell metastasis (24-28). Although first isolated from mineralized bone matrix, OPN can also be synthesized by several other cells, such as cardiomyocytes, vascular endothelial cells, and fibroblasts. OPN has been detected in human atherosclerotic plaques in the aorta, carotid, and coronary arteries, and it has been shown to be implicated in the development and progression of atherosclerosis (29). Increased levels of OPN have been found to be related to the presence and extent of CAD and to restenosis following percutaneous coronary revascularization (29, 30). Leaw et al. (31) have shown that rat carotid neointimal lesions induced by balloon catheter denudation can be reduced by in vivo neutralization of OPN.

Some studies have implicated the role of OPN in postnatal neovascularization, such as increased mRNA expression at the sites of ischemia-induced retinal neovascularization in mice and impaired neovascularization in blunted OPN expression in a murine model of hind limb ischemia (14, 32). In addition, OPN was shown to be associated with tumor-related angiogenesis, metastasis, and healing after bone fractures (33). In our study, OPN levels were higher in the coronary CTO group and were independently associated with better developed coronary collaterals.

A significant number of patients with coronary CTO are either ineligible or demonstrate suboptimal responses to surgical and percutaneous revascularization approaches. A non-invasive approach aimed at promoting the growth of coronary collateral blood vessels has been proposed as a new treatment strategy in such patients (34). Therefore, identifying new molecules that promote the growth of coronary collateral blood vessels is very important. OPN and AGN were widely studied for their angiogenic potential in different disease conditions (23, 26, 32, 33). In the current study, AGN and OPN levels were revealed to be independently associated with the coronary collateral development in patients with coronary CTO. In addition, OPN itself and molecules affecting OPN expression were shown to improve the angiogenic properties of stem cells in recent studies (35, 36). All these findings suggest that these molecules can constitute future therapeutic targets for medical revascularization, and their exact role in coronary collateral development should be clarified in further studies.

Our study has several limitations. First, this is a single-center study, and the small number of the study population has limited some statistical analyses to be performed. Second, this is a hypothesis-generating clinical study, and a mechanistic link between levels of AGN and OPN and the presence of coronary total occlusion and degree of collateral circulation development cannot be proposed with these data.

Conclusion

In conclusion, the present study highlights the association between AGN and OPN levels and coronary collateral circulation in patients with coronary total occlusion. However, the underlying mechanisms remain largely unknown. The results of our study merit further studies to reveal if AGN and OPN are biomarkers or moderators in coronary collateral development.

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B.E., H.Y., M.L.Ş., E.B.K., N.Ö., D.G., K.A., L.T.; Literature search – K.M.G., M.U.Y., D.K., N.Ö., D.G., K.A., L.T.; Writing – K.M.G., M.U.Y., D.K., M.S.B., H.C., B.E., H.Y., M.L.Ş., E.B.K., N.Ö., D.G., K.A., L.T.; Critical review – B.E., H.Y., M.L.Ş., E.B.K., N.Ö., D.G., K.A., L.T.

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