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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The impact of the apelinergic system in coronary collateral formation

Apelinerjik sistemin koroner kollateral oluşumuna etkisi

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ABSTRACT

Background: This study aims to examine the relationship between the development of coronary collateral circulation and serum elabela levels.

Methods: Between January 2020 and December 2021, a total of 50 control individuals (29 males, 21 females; mean age: 63.2±10.0 years; range, 52 to 73 years) with no significant coronary artery disease as confirmed by angiography (Group 1) and 100 patients (55 males, 45 females; mean age: 66.6±9.6 years; range, 56 to 75 years) with coronary artery disease were included. The patients were further divided into two equal groups according to the Rentrop classification as poor (Group 2) and good coronary collateral circulation (Group 3). All groups were compared in terms of several parameters, particularly serum elabela levels.

Results: Serum elabela levels were found to be statistically higher in the group with good collateral than the other groups ($p<0.05$). Low serum elabela levels increased the risk of developing weak collaterals by 2.43 times.

Conclusion: The elabela protein is directly related to good collateral development and can be considered a potential agent for treatment.

Keywords: Apelinergic system, coronary artery disease, coronary collateral, elabela.

ÖZ

Amaç: Bu çalışmada koroner kollateral dolaşım gelişimi ve serum elabela düzeyleri arasındaki ilişki araştırıldı.

Çalışma planı: Ocak 2020 - Aralık 2021 tarihleri arasında anjiyografi ile doğrulandığı üzere önemli bir koroner arter hastalığı olmayan toplam 50 kontrol kişisi (29 erkek, 21 kadın; ort. yaş: 63.2±10.0 yıl; dağılım, 52-73 yıl) ve koroner arter hastalığı olan 100 hasta (55 erkek, 45 kadın; ort. yaş: 66.6±9.6 yıl; dağılım, 56-75 yıl) çalışmaya alındı. Hastalar Rentrop sınıflandırmasına göre kötü (Grup 2) ve iyi koroner kollateral dolaşım (Grup 3) olmak üzere iki eşit gruba ayrıldı. Tüm gruplar serum elabela düzeyleri başta olmak üzere çeşitli parametreler açısından karşılaştırıldı.

Bulgular: İyi kollateral grubunda serum elabela düzeyleri diğer gruplara kıyasla anlamlı düzeyde yüksek bulundu ($p<0.05$). Düşük serum elabela düzeyleri, zayıf kollateral gelişim riskini 2.43 kat artırdı.

Sonuç: Elabela proteini iyi kollateral gelişimi ile doğrudan ilişkili olup, tedavide potansiyel bir ajan olarak düşünülebilir.

Anahtar sözcükler: Apelinerjik sistem, koroner arter hastalığı, koroner kollateral, elabela.

Cardiovascular diseases, particularly coronary artery disease (CAD), are the most common causes of death worldwide.[1] In addition to the elimination of ischemia, different treatments have emerged in recent years. One of these approaches includes studies conducted to increase the efficiency of the collateral system in coronary arteries. In CAD, collateral vessel formation is thought to be triggered in response to ischemia. When angiogenesis and arteriogenesis are initiated by endogenous signals from ischemic tissues,

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collateral vessels are formed. On the other hand, it has been reported that coronary collateral circulation (CCC) can be observed without any stress ischemia.[2] The metabolic factors that induce or modulate these processes have not been fully elucidated, yet.

In studies on the effects of the apelinergic (APJ) system on cardiovascular diseases, APJ ligands such as apelin and elabela (ELA) have been shown to play a key role in many metabolic events.[3,4] It has been demonstrated that the APJ system is the part of a protective mechanism in cardiovascular diseases such as myocardial infarction, pulmonary hypertension (HT), and heart failure.[5] This system was previously thought to be regulated only by the apelin protein. However, it has been recently discovered that the ELA protein (also called toddler or apela), previously known as an orphan ligand, binds to APJ receptors and has important functions.[6] In a recent study, the APJ system has been found to be functional, since fetal life with the discovery of the ELA gene sequence.[7] Wang et al.[8] reported that ELA deficiency also caused cardiac deformities in the embryonic age, similar to the apelin protein. Studies on ELA protein-deficient mice have shown that ELA protein protects against cardiac dysfunction due to reperfusion damage after myocardial infarction, and ELA deficiency has negative effects on left ventricle remodeling.[9] In parallel with these results, the myocardial gene sequence with the highest upregulation in patients implanted with a left ventricular assist device was observed in the APJ system.[10] Elabela is also known to increase myocardial contraction and vasodilation in the coronary vascular bed, similar to apelin protein. In addition, the ELA protein has preventive effects on volume overload and HT due to its antagonist effects on the renin-angiotensin-aldosterone system.[11] In an *in vivo* study, Wang et al.[8] demonstrated that ELA could stimulate angiogenesis through the APJ ligand. In the present study, we aimed to examine the relationship between the development of CCC and serum ELA levels.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at Adana Şehir Training and Research Hospital, Department of Cardiovascular Surgery between January 2020 and December 2021. A total of 50 control individuals (29 males, 21 females; mean age: 63.2±10.0 years; range, 52 to 73 years) with no significant CAD as confirmed by angiography (Group 1) and 100 patients (55 males, 45 females; mean age: 66.6±9.6 years; range, 56 to 75 years) with CAD (≥1 chronic total occlusion [CTO] lesion) were included. The patients were further divided into two groups according to the Rentrop classification as poor (Group 2) and good CCC (Group 3). The Rentrop classification was a system used to classify collateral formation in coronary arteries. According to this classification, 0; no visible signs of collateral system circulation, 1; filling of the lateral branches without filling in the epicardial artery, 2; partial filling of the epicardial artery by collateral circulation, and 3; complete filling of the epicardial artery through collateral circulation.[12] The control group consisted of 50 individuals, the poor CCC group consisted of 50 patients with a Rentrop score of 0 and 1, and the good CCC group consisted of 50 patients with a Rentrop score of 2 and 3. Patients with a medical history of percutaneous coronary intervention or coronary artery surgery were excluded. Echocardiographic evaluations, laboratory results, and medical histories of all patients were also recorded.

All blood samples of the patients were obtained within the first 24 h after admission. Complete blood count, creatinine, glomerular filtration rate (GFR), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, albumin, N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitive C-reactive protein, and serum ELA levels were analyzed using routine laboratory tests. Serum ELA levels were measured using commercial kits (Sunred Biological Technology, Shanghai, China). These kits use a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to measure the level of ELA-32 in blood samples. Inter-assay coefficient of variation (CV) is a measure of the variance between runs of sample replicates on different plates that can be used to assess plate-to-plate consistency. As a general guideline, to gauge the overall reliability of your immunoassay results, inter-assay CV% should be less than 15% while intra-assay CV% should be less than 10%. According to the manufacturer's instructions, this assay has an inter-assay CV of <12% and an intra-assay CV of 10%.

The Judkins's technique was performed as a standard in routine coronary angiography. A minimum of two planes were recorded for each coronary artery system evaluation. These recordings were once again reviewed by a single cardiologist and a cardiovascular surgeon to identify the level of collateral circulation. Two-dimensional transthoracic echocardiographic and Doppler examinations were performed using an echocardiography device (EPIQ 7; Philips

Healthcare, Andover, MA, USA). Left ventricular ejection fraction (LVEF) was calculated using the Biplane Simpson Method.[11] Geometric parameters of the left ventricle and left atrium were calculated in accordance with the standards of the American Society of Echocardiography.[13]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min-max), or number and frequency, where applicable. The skewness and kurtosis values were examined together with the Kolmogorov-Smirnov and Shapiro-Wilk tests to perform controls for compliance with normal distribution. The Welch, one-way analysis of variance (ANOVA), chi-square, and Kruskal-Wallis H tests were used for the comparison of the groups. The Games-Howell, Tukey honestly significant difference (HSD), and Dunn tests were used for post-hoc analysis, where necessary. The multivariate regression method was used to identify the risk coefficients among the three groups. A p value of <0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference in demographic data among the groups (p>0.05). However, the incidence of chronic obstructive pulmonary disease was higher in the group with good collateral than the other group (p=0.009) (Table 1).

When blood ELA levels, which formed the basis of our study, were compared, higher values were found in the good collateral group than both the control group and the poor collateral group (p<0.001). There was no significant difference between the poor collateral group and the control group (p>0.05) (Table 2). Furthermore, multivariate regression analysis was performed to examine the relationship between blood ELA levels and the development of collateral coronary vessels. Accordingly, we found that low blood ELA levels increased the risk of developing poor collaterals by 2.43 times (Table 3). In addition, the incidence of CTO in the right coronary

Table 1. Patient characteristics and presence of comorbid diseases among the control, poor collateral, and good collateral groups

	Control (n=50)			Poor collateral (n=50)			Good collateral (n=50)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			63.2±10.0			65.8±9.3			67.5±9.9	0.082*
Sex										
Male	29	34.5		27	32.1		28	33.3		0.922†
Diabetes mellitus	12	23.1		19	36.5		21	40.4		0.139†
Hypertension	10	20.4		17	34.7		22	44.9		0.037†
COPD	5	14.3		12	34.3		18	51.4		0.009†
Smoking	12	21.8		21	38.2		22	40.0		0.073†

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; * Analysis of variance; † Pearson's chi-squared test.

Table 2. Elabela, NT-ProBNP, LVEF, and CTO on RCA among to groups

	Control (n=50)	Poor collateral (n=50)	Good collateral (n=50)		Control-poor collateral	Control-good collateral	Poor-good collateral
	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*	*p*
Elabela (ng/mL)	2.604±0.966	3.624±0.356	12.563±3.102	<0.001*	<0.001	<0.001	<0.001
NT-ProBNP (pg/mL)	13.056±1.413	52.276±2.134	72.210±1.661	<0.001*	<0.001	<0.001	<0.001
LVEF (%)	57.82±4.521	49.58±2.704	43.84±3.951	<0.001*	<0.001	<0.001	<0.001
CTO on RCA	0	16 (24.2%)	34 (68%)	<0.001†			

SD: Standard deviation; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: Left ventricular ejection fraction; CTO: Chronic total occlusion; RCA: Right coronary artery; * Bonferroni test; † Pearson's chi-square test.

Table 3. Multivariate regression analysis results

	β	SE	Wald	df	*p*	OR	95% CI for OR	
							Lower	Upper
Control	-1.443	0.264	29,905	1	**<0.001**	0.236	0.141	0.396
Good collateral	0.888	0.158	31,594	1	**<0.001**	2.431	1.783	3.313

β: Regression coefficient; SE: Standard error; Wald: Standardized regression coefficient; CI: Confidence interval; OR: Odds ratio; df: Degrees of freedom. Bold sections are statistically significant (p<0.05).

artery was found to be statistically significantly higher in the good collateral group than in the other groups (p<0.001). When all groups were compared in terms of LVEF, LVEF values of the group with good collateral were observed to be lower and this difference was statistically significant (LVEF% control group: 57.82±4.521, poor collateral group: 49.58±2.704, good collateral group: 43.84±3.951, p<0.001). The NT-proBNP (pg/mL) levels were also statistically higher in the good collateral group than in the other groups (p<0.001).

DISCUSSION

In the present study, we examined the relationship between the development of CCC and serum ELA levels. Our study results revealed a positive relationship between the presence of collateral vessels in coronary arteries and serum ELA levels. The advancement in the treatment of CAD is currently pushing the limits of revascularization procedures and medical treatment options. A considerably large population is either not suitable for conventional treatments or are not able to benefit from these treatments due to their additional diseases, as well as the anatomical prevalence of the disease. Alternative treatment options that would increase the nutrition of the ischemic heart by increasing the CCC are promising among the alternative treatments.[14] Although clinical studies and treatment approaches have been trialed, the process of collateral circulation formation and development have not been fully clarified, yet.

It is believed that the collateral system develops as an adaptive mechanism. This adaptation can be regarded as a metabolic response of the myocardium to an ischemic condition. Nonetheless, different levels of collateral development observed in patients with similar lesions in the coronary arteries suggest that there are multiple mechanisms coexisting in the process. The causality relationship underlying these differences may be the answer to questions about the formation of CCC. The collateral system can develop in two ways: angiogenesis, which involves the formation of new vessels, and arteriogenesis, which refers to the maturation of existing collateral vessels. While hypoxia is the main trigger in angiogenesis, the main mechanism in arteriogenesis occurs with the mechanical pressure created by shear stress in fluids. Vasodilation and enlargement of the vascular wall are observed in both metabolic processes. Endothelial cells respond to this enlargement with proliferation, and new vascular pathways are formed or existing vascular structures are further improved.[15,16] Arteriogenesis, which occurs with the development of vascular smooth cells in coronary arteries, has a more important role.[14] Regardless of the way it develops, it has been demonstrated in many clinical studies that an advanced collateral system has positive effects on the course of cardiovascular diseases.[17,18]

While interpreting the results of our study, it is important to consider that the demographic characteristics of the patients are similar. This results in a more objective evaluation of the results of our study. It has been shown in many studies that factors such as diabetes mellitus, HT, and advanced age affect the development of collateral.[19,20] The homogeneity of the groups in terms of these parameters enables us to examine the relationship of ELA, which is the main subject of our study, with the development of coronary collateral in a much simpler way. On the other hand, there are differences in some echocardiographic and blood parameters due to the mechanisms during the formation of coronary collateral. To illustrate, our results regarding LVEF are quite interesting. There are studies that associate good coronary collateral development with better left ventricular functions, while there are also publications claiming the opposite.[20,21] In the study of Kadı et al.,[20] patients with a good collateral development had better LVEF. The authors hypothesized that the extensive collateral network would naturally result in better perfusion as the reason for this. On the other hand, in another study, CTO was required

for the development of the collateral network and that the resulting CTO impaired left ventricular functions due to previous myocardial infarctions.[21] In other words, pathologies that cause good collateral development may have caused deterioration of left ventricular functions. In our study, similar to the study of Tandoğan et al.,[21] left ventricular functions were worse in the group with a good collateral development. Another result that supports this is that more RCA CTO was observed in the group with a good collateral development. As a result, both better collaterals developed, while left ventricular functions could be impaired due to possible previous silent infarcts. In relation to this, NT-proBNP levels were also found to be higher in the good collateral group, particularly in the worse left ventricle group, compared to the other group. This can be attributed to the increased wall tension in the group with poor left ventricle, as it has been shown in many studies that NT-proBNP levels increase, particularly as myocardial tension increases.[20,21]

Considering the effects of the APJ system on angiogenesis and the regulatory roles of ELA protein in the cardiovascular system, it is reasonable to associate it with the formation of coronary collaterals. In this context, the presence of both APJ receptors and ELA protein in vascular smooth muscle cells and endothelium is strong evidence supporting this inference.[19-21] On the other hand, the mechanisms of these effects of ELA are also clear. Namely, ELA is thought to be important for heart formation and migration of cardiac progenitor cells for heart development during embryonic development.[22] This theory has been supported by many *in vivo* studies.[23,24] In general, these studies have shown that ELA continuously supports cardiac myocyte development, stimulates self-renewal of embryonic stem cells, and triggers coronary angiogenesis in relation to these findings. The results of our study also demonstrated that the serum ELA levels were higher in patients with collateral circulation, indicating that there are more intense APJ activities observed in these patients.

In addition to theoretical studies on ELA protein as a treatment method, animal experiments have shown that it reduces ischemia-reperfusion injury in the acute-subacute period of myocardial ischemia.[25] In a study, infarct areas were more limited in mice given ELA infusion, and cardiac damage markers (lactate dehydrogenase, creatine kinase-myoglobin binding, troponin I) were at lower levels. Exactly on which metabolic activity all these outputs affect is not a subject that has been fully clarified, but it has not been ignored that it has made a positive contribution through collateral circulation.[25] The need for alternative treatment methods has been increasing for patients who have lost the chance of revascularization due to common CAD or additional diseases. The therapeutic idea of stimulating the formation of collateral arteries exogenously is one of the most important potential treatment alternatives that have been discussed and studied for these patients in recent years.[26,27] Some studies have shown better ventricular functions, as well as decreased angina attacks with the increased collateral circulation.[28] Even if it does not promise an absolute solution for the patients, it can contribute significantly to the increase in the quality of life.

Nonetheless, there are some limitations to this study. First, it has a single-center design with a relatively small sample size. Second, although biochemical measurements of serum ELA levels were performed, no receptor-level measurements were able to be performed in the target organ tissue.

In conclusion, elabela protein is associated with good coronary collateral development, possibly as the part of the endogenous response of the apelinergic system to ischemia. Based on these findings, we believe that elabela protein can be a guide in both the decision-making and direct treatment of coronary artery disease. Further well-designed animal and clinical studies are needed to confirm these findings.

Ethics Committee Approval: The study protocol was approved by the Cukurova University Ethics Committee (date: 04.09.2019, no: 54). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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