# The İmpact Of The Apelinergic System In Coronary Collateral Formation

**Ibrahim Ozsoyler** ( iozsoyler@gmail.com )
University of Health Sciences Adana City Training and Research Hospital
**Haci Ali Ucak**
University of Health Sciences Adana City Training and Research Hospital
**Tolga Onur Badak**
University of Health Sciences Adana City Training and Research Hospital
**Ahmet Cakallioglu**
University of Health Sciences Adana City Training and Research Hospital
**Muhammed Bayraktar**
Niğde University
**Ahmet Suha Arslan**
University of Health Sciences Adana City Training and Research Hospital

**Research Article**

**Keywords:** Elabela, Coronary Collateral, Coronary Artery Disease, Apelinergic System

**Posted Date:** March 3rd, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1355665/v1

# Abstract

**Background:** İn coronary artery disease, the positive contribution of the presence of coronary collateral circulation to the course of the disease is known. As for the factors that trigger the formation of collateral circulation and interactions at the cellular level, no satisfactory results have yet been reached. Studies on this issue will also pave the way for potential treatment opportunities in the future. The aim of this study is to try to determine the relationship between coronary collateral circulation and elabela and apelinergic system.

**Methods:** This is a cross sectional study. Totally 150 subjects were included the study. Demographic data, laboratory test data, and comorbidities were collected from the hospital data. Welch, One Way Anova, Chi-Square, and Kruskal-Wallis H tests were used for comparison of the groups. Games-Howell, Tukey HSD, and Dunn tests were used for post-hoc analysis where necessary.

**Results:** Evaluating the differences between the groups in terms of the parameters examined. Looking at which groups the differences arise from; it was observed that the statistically significant difference observed for elabela, HDL-C, NT-ProBNP, LVEF and HS-C-Reactive protein was between all groups separately.

**Conclusions:** In this study, we aim to reveal a positive relationship between the development of coronary collateral vessels and apelinergic systems. Our results indicated that Elabela protein could be evaluated as a potential agent for treatment.


# Background

Cardiovascular diseases, particularly coronary artery disease, are the most common causes of death in the world. In diagnosed cases, recovery can be achieved by revascularization in percutaneous methods or coronary artery bypass grafting (CABG) surgery in most of the patients. However, up to 20% of the patient population may not be suitable for either of the procedures due to comorbid factors and diffuse atherosclerosis.(1) More aggressive medical treatment options are performed in these patients; however, this palliative approach is often far from providing satisfactory results. In recent years, there have been different approaches to the prevention and correction of myocardial ischemia. One of these approaches includes the studies conducted for increasing the efficiency of the collateral system in coronary arteries. Collateral circulation is a natural anastomosis system that extends from an artery with healthy or sufficient flow to the occluded artery, and increases the blood supply in the target vessel. In coronary artery disease, it is thought that the formation of collateral vessels is triggered in response to ischemia. When angiogenesis and arteriogenesis are triggered by the endogenous signals coming from the ischemic tissues, this leads to the formation of collateral vessels. On the other hand, it has been previously reported that coronary collateral circulation (CCC) can be monitored without any stress ischemia.(2) The metabolic factors that induce or modulate these processes have not been fully clarified yet.

In studies on the effects of the apelinergic (APJ) system on cardiovascular diseases, APJ ligands such as apelin and Elabela were found to play important roles in many metabolic events.(3–5) It was previously demonstrated that the APJ system was a part of a mechanism for protection from the effects of the disease in cardiovascular diseases, such as myocardial infarction, pulmonary hypertension and heart failure.(6, 7) It was previously assumed that this system was regulated only by the apelin protein. However, it has recently been discovered that elabela protein (also called toddler or apela), which was previously known as an orphan ligand, binds to APJ receptors, and has important functions.(8) Zhang et al. reported that, Elabela deficiency also caused cardiac deformities in the embryonic age, similar to the apelin protein.(9) Elabela is also known to increase myocardial contraction and vasodilation in the coronary vascular bed, similar to apelin protein. In addition, the Elabela protein has preventive effects on volume overload and hypertension, due to the antagonist effects on the renin angiotensin aldosterone system.(10) In an in vivo study, Wang et al. demonstrated that elabela could stimulate angiogenesis through the APJ ligand. In this study, we aimed to examine the relationship between the development of CCC and serum elabela levels.

# Methods

This study was planned as cross sectional. The study was approved by the local ethics committee of Çukurova University (number 91/ September 4, 2019). All written informed consents of the study signed by each subject. All procedures were performed in accordance with relevant guidelines. A total of 150 patients were included. Patients with a medical history of percutaneous coronary intervention or coronary artery surgery were not included in the study. Successful percutaneous coronary intervention was performed in all patients who required a procedure. The medical treatment of the patients was carried out in accordance with the guidelines. Cardiogenic shock was not observed in any patient. All patients and controls were questioned about demographic variables. 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 hours after admission. The values regarding complete blood count, creatinine, glomerular filtration rate (GFR), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, albumin, N terminal pro-BNP (NT-proBNP), high-sensitive C reactive protein (Hs-CRP) and serum Elabela levels were determined with routine laboratory tests. Serum Elabela levels were determined 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 Elabela-32 in blood samples. According to the manufacturer, this assay has inter-assay coefficients of variation < 12% and intra-assay coefficients of variation of 10%.

Judkins 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 cardiologist and a cardiovascular surgeon in order to determine the level of collateral circulation. Two-dimensional transthoracic echocardiographic and doppler evaluations were performed using an echocardiography device (EPIQ 7; Philips Healthcare, Andover, MA). 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 American Society of Echocardiography.(12)

Statistical Analyses

Data were analyzed with SPSS version 22. Descriptive statistics were presented as mean ± standard deviation, median (min-max), and frequency distribution (percentages). The skewness and kurtosis values were examined together with the Kolmogorov-Smirnov and Shapiro-Wilk tests to perform controls for compliance with normal distribution. Welch, One Way Anova, Chi-Square, and Kruskal-Wallis H tests were used for comparison of the groups. Games-Howell, Tukey HSD, and Dunn tests were used for post-hoc analysis where necessary. Values of $p < 0.05$ were considered statistically significant.

# Results

This cross-sectional study included 50 control subjects with no significant coronary artery stenosis confirmed in angiography and 100 patients with coronary artery disease [≥ 1 chronic total occlusion (CTO) lesion] in two groups (poor and good CCC). Control group of the study included the 50 individuals (Group 1), poor CCC group included 50 patients with a Rentrop score of 0 and 1 (Group 3), and the good CCC group consisted of the 50 patients with a Rentrop score of 2 and 3 (Group 3).

When the differences among the groups in terms of patient characteristics and the presence of accompanying diseases were examined; it was observed that the body mass index value ($p < 0.001$), hypertension disease ($p = 0.037$) and chronic obstructive pulmonary disease ($p = 0.009$) caused a statistically significant difference among the groups. In the posthoc analysis conducted to examine which groups caused the difference created by the body mass index value; it was seen that it originated from the control group and the poor collateral group ($p = 0.018$), the control group and the good collateral group ($p < 0.001$) (Table 1).

Table 1
Differences among the groups in terms of the patients characteristics and presence of co-morbid diseases

| | **Control (n = 50)** | **Poor collateral (n = 50)** | **Good collateral (n = 50)** | **p** |
|---|---|---|---|---|
| Body Mass Index ($kg/m^2$) | 23.220 ± 3.039 | 24.740 ± 2.414 | 26.040 ± 2.762 | **< 0.001[a]** |
| Post-hoc test[x]: C vs PC (**p = 0.018**), C vs GC (**p < 0.001**), PC vs GC (p = 0.051) | | | | |
| Age (years) | 63.160 ± 9.980 | 65.760 ± 9.290 | 67.520 ± 9.852 | 0.082[b] |
| Gender (male) | 29(34.5%) | 27(32.1%) | 28(33.3%) | 0.922[c] |
| DM | 12(23.1%) | 19(36.5%) | 21(40.4%) | 0.139[c] |
| HT | 10(20.4%) | 17(34.7%) | 22(44.9%) | 0.037[c] |
| COPD | 5(14.3%) | 12(34.3%) | 18(51.4%) | 0.009[c] |
| Smoking | 12(21.8%) | 21(38.2%) | 22(40.0%) | 0.073[c] |
| Data presented as mean ± SD, median(min-max), and number of patients (%). a: Welch, b: ANOVA, c: Pearson's Chi-Square x: Games-Howell | | | | |

Evaluating the differences between the groups in terms of the parameters examined, it was seen that there were statistically significant differences among the groups in terms of all parameters ($p < 0.001$) except left atrium diameter ($p = 0.278$). Looking at which groups the differences arise from; it was observed that the statistically significant difference observed for elabela (Fig. 1), HDL-C, NT-ProBNP, LVEF, and HS-C-Reactive protein was between all groups separately. The group differences originating from in terms of other parameters and their p values can be seen in Table 2.

Table 2
Differences Among the Groups İn Terms of The Parameters Being Examined

| | Control (n = 50) | Poor collateral (n = 50) | Good collateral (n = 50) | p |
|---|---|---|---|---|
| **Elabela (ng/mL)** | 2.604 ± 0.966 | 3.624 ± 0.356 | 12.563 ± 3.102 | **< 0.001**[a] |
| Post-hoc test[x]: C vs. PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (**p < 0.001**) | | | | |
| **Left atrium diameter (mm)** | 3.049 ± 0.467 | 2.881 ± 0.616 | 3.027 ± 0.403 | 0.278[a] |
| **Hemoglobin (g/dL)** | 14.162 ± 1.064 | 13.064 ± 1.478 | 12.940 ± 1.221 | **< 0.001**[b] |
| Post-hoc test[y]: C vs. PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (p = 0.876) | | | | |
| **eGFR** | 100.632 ± 11.335 | 80.036 ± 8.066 | 80.014 ± 11.078 | **< 0.001**[b] |
| Post-hoc test[y]: C vs. PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (p = 1.000) | | | | |
| **HDL-C (mg/dL)** | 48.040 ± 3.493 | 40.600 ± 6.845 | 37.660 ± 5.053 | **< 0.001**[a] |
| Post-hoc test[x]: C vs PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (**p = 0.043**) | | | | |
| **NT-ProBNP (pg/mL)** | 13.056 ± 1.413 | 52.276 ± 2.134 | 72.210 ± 1.661 | **< 0.001**[a] |
| Post-hoc test[x]: C vs PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (**p < 0.001**) | | | | |
| **LVEF (%)** | 57.82 ± 4.521 | 49.58 ± 2.704 | 43.84 ± 3.951 | **< 0.001**[a] |
| Post-hoc test[x]: C vs PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (**p < 0.001**) | | | | |
| **WBC $\times 10^9$/L** | 9.1(7.9–10.9) | 9(6.7–10.9) | 9.9(8-17.9) | **< 0.001**[c] |
| Post-hoc test[z]: C vs PC (p = 0.962), C vs GC (**p < 0.001**), PC vs GC (**p < 0.001**) | | | | |
| **Platelet Count (10/µL)** | 229.5(173–276) | 209.5(150–410) | 238(202–410) | **< 0.001**[c] |
| Post-hoc test[z]: C vs PC (p = 0.130), C vs GC (p = 0.82), PC vs GC (**p < 0.001**) | | | | |
| **LDL-C (mg/dL)** | 126(102–140) | 138(95–344) | 139(122–302) | **< 0.001**[c] |
| Post-hoc test[z]: C vs PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (p = 1.000) | | | | |

| | Control (n = 50) | Poor collateral (n = 50) | Good collateral (n = 50) | p |
|---|---|---|---|---|
| **Triglyceride (mg/dL)** | 112(91–130) | 160(130–564) | 164(140–824) | **< 0.001[c]** |
| Post-hoc test[z]: C vs PC (**p < 0.001**), C vs GC (**p < 0.001**), PC vs GC (p = 1.000) | | | | |
| **Creatinine** | 0.95(0.60–1.29) | 1(0–1) | 1.25(0.93–3.25) | **< 0.001[c]** |
| Post-hoc test[z]: C vs PC (p = 0.054), C vs GC (**p < 0.001**), PC vs GC (**p < 0.001**) | | | | |
| **HS-C-Reactive Protein (mg/L)** | 0.84(0.32–1.47) | 1.16(1.01–1.30) | 3.06(1.81–23.74) | **< 0.001[c]** |
| Post-hoc test[z]: C vs PC (**p = 0.003**), C vs GC (**p < 0.001**), PC vs GC (**p < 0.001**) | | | | |
| **Serum Albumin** | 3.19(2.41–4.05) | 2.17(1.59–1.97) | 3.57(2.70-.27) | **< 0.001[c]** |
| Post-hoc test[z]: C vs PC (p = 0.066), C vs GC (**p = 0.007**), PC vs GC (**p < 0.001**) | | | | |
| **CTO on RCA** | 0 | 16(24.2%) | 34(68%) | **< 0.001[d]** |
| Data presented as mean ± SD, median(min-max), and number of patients (%).<br>a: Welch, b: ANOVA, c: Kruskall-Wallis H, d: Pearson's Chi-Square<br>x:Games-Howell, y:Tukey HSD, z:Dunn | | | | |

# Discussion

The results of our study revealed a positive relationship between the presence of collateral vessels in coronary arteries and the serum Elabela levels. The advancement in the treatment of coronary artery disease is now 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 will increase the nutrition of the ischemic heart by increasing the coronary collateral circulation are promising among the alternative treatments.(13–15) Although the trials of clinical studies and treatment approaches are performed on the subject, the how collateral circulation is formed and how it develops have still not been fully clarified.

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. The first one is called angiogenesis, which involves the formation of new vessels; and the second one is the 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 the 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.(16) Arteriogenesis, which occurs with the development of vascular smooth cells in coronary arteries, has a more important role.(17) 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.(18, 19)

Considering the effects of the apelinergic system on angiogenesis and the regulatory roles of Elabela protein in the cardiovascular system, it is reasonable to associate it with the formation of coronary collaterals. At this point, the presence of both APJ receptors and Elabela protein in vascular smooth muscle cells and endothelium is important evidence supporting this inference.(20, 21) The results of our study also demonstrated that the serum Elabela levels were higher in patients with collateral circulation. This indicates that there were more intense apelinergic activities observed in these patients. The results of the study showed that there is a significant correlation between hypertension and COPD and coronary collaterals. It may be due to the ischemic stress caused by both pathological conditions on the coronary circulation or to have similar epidemiological features. In a study by Xu et al., they found that the apelinergic system was induced by hypertension, and the incidence of preeclampsia increased in its deficiency, and suggested that it should be considered as a treatment option.(22)

The need for alternative treatment methods is increasing for patients, who have lost the chance of revascularization due to common coronary artery disease 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.(23–25) Some studies have reported better ventricular functions as well as decreased angina attacks with increased collateral circulation.(26) Even if it does not promise an absolute solution for the patients, it can contribute significantly to the increase in the quality of life.

# Conclusion

In this study, we tried to reveal a possible positive relationship between the collateral and apelinergic systems. Our results indicated that Elabela protein could be evaluated as a potential agent for treatment. Significantly different levels of Elabela between the control group and the patients with coronary artery disease obtained in the present study, which was conducted with a limited number of participants, indicates that the apelinergic system is part of an endogenous response to ischemia. It has already been demonstrated in previous studies that serum levels are significantly higher patients with heart failure and acute coronary syndrome compared to the healthy controls.(27, 28) The difference in Elabela levels was

also observed between patients with poor CCC and the good CCC group; and this supports the idea that at least part of this adaptive response was associated with collateral circulation. Despite the fact that the developments are promising, there is a need for further progress in this regard.

# List Of Abbreviations

Coronary Artery Bypass Grafting (CABG)

Coronary Collateral Circulation (CCC)

Apelinergic (APJ)

Chronic Total Occlusion (CTO)

Glomerular Filtration Rate (GFR)

Low Density Lipoprotein (LDL)

High Density Lipoprotein (HDL)

N Terminal Pro-BNP (NT-Pro BNP)

High-Sensitive C Reactive Protein (Hs-CRP)

Left Ventricular Ejection Fraction (LVEF)

# Declarations

### Disclosure of conflict of interest

All authors certify that there is no actual or potential conflict of interest in relation to this article.

All authors certify that there is no funding for this research.

### Ethics approval and consent to participate:

The study was approved by the local ethics committee of Çukurova University (number 91/ September 4, 2019). Prior to data collection, written informed consent was obtained from all participants.

### Consent for publication:

Not applicable. This manuscript does not contain data from any individual person

### Availability of data and materials:

All data generated or analysed during this study are included in this published article.

**Competing interests:**

The authors declare that they have no competing interests

**Funding:**

We have not received any financial support from any institution/government; hence, the operation of the research is solely financed by the handling fee received from the authors.

**Acknowledgement:**

Not applicable

**Authors' contributions**

**OI:** Conceptualization, methodology, investigation, formal analysis, writing-original draft, supervision, revision and review

**UH:** Conceptualization, methodology, investigation, Coronary angiography scan, formal analysis, writing-original draft and review

**BT**: Coronary angiography scan and data analysis

**CA**: Coronary angiography scan, methodology, data collection and data analysis

**BM:** Data analysis, formal analysis, writing-original draft

**AA:** Coronary angiography scan, data collection

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# Figures

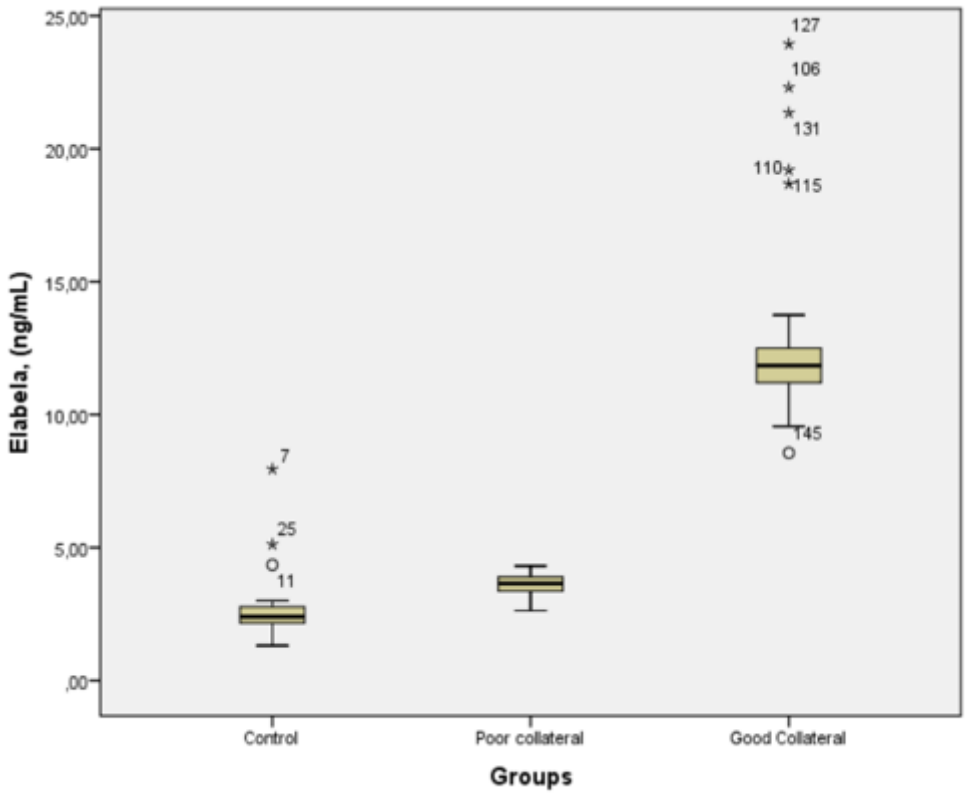


**Figure 1**

Box-plot representation for elabela level changes by groups