

# Determinants of coronary collateral circulation in patients with coronary artery disease

*Koroner arter hastalığı olan hastalarda koroner kollateral gelişiminin belirteçleri*

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## ABSTRACT

**Objective:** This study aims to identify possible determinants of coronary collaterals in patients with severe coronary artery disease.

**Methods:** The current study has a retrospective cohort design. Seventy four patients with  $\geq 90\%$  stenosis or total occlusion of the left anterior descending artery (LAD) were enrolled; coronary collateral grades, high-sensitive C-reactive protein (hs-CRP), fibrinogen, protein C and S, lipids, uric acid levels and medications applied before coronary angiography were noted and compared. Multiple logistic regression analysis was used for the multivariate analyses of independent variables associated with the development of adequate coronary collateral vessels.

**Results:** The presence of coronary collaterals was significantly higher in males ( $p=0.018$ ), with higher hs-CRP ( $p=0.023$ ), prior statin use ( $p=0.022$ ), and higher Gensini scores ( $p<0.001$ ). In multiple logistic regression analysis, hs-CRP levels (OR=0.94, 95.0% CI=0.883-1.000,  $p=0.048$ ), male gender (OR=4.73, 95.0% CI=1.441-15.539,  $p=0.010$ ) and prior statin usage (OR=4.70, 95.0% CI=1.264-17.452,  $p=0.021$ ) were identified as independent predictors of coronary collateral development.

**Conclusion:** Male gender, prior statin usage, and higher hs-CRP levels are determinants of coronary collaterals in patients with coronary artery disease. (*Anadolu Kardiyol Derg 2013; 13: 146-51*)

**Key words:** Coronary collateral circulation, coronary artery disease, high-sensitivity C-reactive protein, regression analysis

## ÖZET

**Amaç:** Bu çalışmada ciddi koroner arter hastalığı olanlarda koroner kollateral gelişimini sağlayan muhtemel nedenler araştırılmıştır.

**Yöntemler:** Bu çalışma retrospektif kohort dizayna sahiptir. Sol ön inen arterde (SÖİA)-%90 ve daha fazla darlığı olan ya da (SÖİA) arteri tamamen tıkalı olan 74 hasta çalışmaya alınmıştır. Hastaların yüksek duyarlılık C-reaktif protein (hs-CRP), fibrinojen, protein C ve S, lipid değerleri, ürik asit düzeyleri ile kullandığı ilaçlar tespit edilmiş ve koroner kollateral gelişimine göre karşılaştırılmıştır. Yeterli koroner kollateral gelişimi ile ilişkili bağımsız değişkenlerin belirlenmesinde çoklu lojistik regresyon analizi kullanılmıştır.

**Bulgular:** Koroner kollateral gelişimi, erkek cinsiyette ( $p=0.018$ ), önceden statin kullananlarda ( $p=0.022$ ), yüksek hs-CRP düzeyi olanlarda ( $p=0.023$ ) ve yüksek Gensini skoruna ( $p<0.001$ ) sahip olan kişilerde daha fazla tespit edildi. Çoklu lojistik regresyon analizinde; hs-CRP düzeyleri (OR=0.94, %95.0 CI=0.883-1.000,  $p=0.048$ ), erkek cinsiyet (OR=4.73, %95.0 CI=1.441-15.539,  $p=0.010$ ) ve önceden statin kullanımı (OR=4.70, %95.0 CI=1.264-17.452,  $p=0.021$ ) koroner kollateral gelişiminin bağımsız belirleyicileri olarak tespit edildi.

**Sonuç:** Koroner arter hastalığı olanlarda erkek cinsiyet, statin kullanımı ve yüksek hs-CRP düzeyleri koroner kollateral gelişiminin belirleyicileridir. (*Anadolu Kardiyol Derg 2013; 13: 146-51*)

**Anahtar kelimeler:** Koroner kollateral dolaşım, koroner arter hastalığı, yüksek duyarlılık C-reaktif protein, regresyon analizi

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## Introduction

Severe coronary artery stenosis or total occlusions are frequently observed in patients with stable and unstable coronary artery disease (CAD). Among these, some patients with a similar degree of angiographic coronary stenosis experienced more severe symptoms of coronary ischemia than others. This might lead to angina, shortness of breath, quality of life impairment, left ventricular dysfunction, and worsening of prognosis.

Coronary collateral vessels (CC), the remnants of the embryonic arterial system, can develop in the heart as an adaptation to ischemia (1). True collateral vessels are not seen angiographically in normal hearts, and coronary arteries must be occluded 99% or 100% for CC to be visible (2). Collaterals are capable of blood supply to a myocardial area jeopardized by ischemia. Because they can help to preserve myocardial function by reducing infarct size (3), and may provide a survival benefit (4-6), it is important to know which factors contribute to their development. However, there is limited information on the factors affecting the development of CC. Although coronary lesion severity has been shown to be an independent pathogenetic variable related to collateral flow, there are interindividual differences in the number and extent of collateral vessels among patients with a similar degree of coronary atherosclerosis (7).

Numerous studies have been published about the effects of CC development on mortality and morbidity in patients with CAD (3-6). However, only a few studies about factors influencing the development of CC are available, and majority of them focused on the relation between inflammation and CC development (8-10).

The aim of the study was to define the determinants of CC development such as demographic characteristics (age and gender), inflammation and coagulation parameters [high-sensitive C-reactive protein (hs-CRP), lipid profile, uric acid, protein C, protein S and fibrinogen], co-morbidities (hypertension, diabetes mellitus and metabolic syndrome) and concomitant drug usage in patients with significant CAD.

## Methods

### Study design

This study has a retrospective cohort design.

### Clinical data collection

From January to April 2012, 74 consecutive patients (46 men, 28 women) in two different institutions with greater than/or equal to 90% in the left anterior descending artery (LAD) stenosis with TIMI Grade Flow 0-2 were enrolled to this study and evaluated. All patients had normal/or less than 50% stenosis in the right coronary, left circumflex, diagonal and septal arteries. All patients had stable anginal symptoms and/or positive stress test results or electrocardiographic changes indicating ischemia. Clinical information, including age, weight, gender, and any data known to influence development of collaterals-such as

current medications, history of hypertension and diabetes mellitus, complete blood count, serum cholesterol, and fasting glucose levels-was documented. Patients were excluded if they had a recent history (i.e. a history of less than one month) of acute coronary syndrome, previous coronary intervention, NYHA class III-IV heart failure, atrial fibrillation, severe valvular heart disease, presence of co-existent inflammatory disease (e.g. rheumatoid arthritis), renal failure, severe hepatic diseases, or pregnancy. The study was approved by the regional ethics committee, and all patients gave written informed consent.

### Definitions

Patients were defined as hypertensive if their blood pressure was  $\geq 140/90$  mmHg, or if they were taking any antihypertensive medications. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) criteria were used for the definition of metabolic syndrome (11). Diabetes mellitus was defined as the presence of a history of antidiabetic medication usage, or a fasting glucose level above 126 mg/dL. Patients were considered to have hyperlipidemia if their total cholesterol was  $\geq 200$  mg/dL, or if they were taking lipid-lowering medication.

### Blood samples and analyses

Fasting venous blood samples were collected before coronary angiography for biochemical tests. Serum glucose, triglyceride, total-cholesterol, low density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, fibrinogen, protein C, protein S, and uric acid levels were measured using an autoanalyzer (COBAS MIRA, Roche, Switzerland). For hs-CRP analysis, blood samples were centrifuged, and serum was removed and stored at  $-80^{\circ}\text{C}$  until the assay had been performed. High-sensitivity C-reactive protein was analyzed using a commercially available test (N-Latex CRP II, Dade Behring Marburg GmbH, Marburg, Germany).

### Coronary angiography and grading of coronary collaterals

Selective coronary angiography was performed in multiple orthogonal projections using the Judkins technique. Angiograms were reviewed by an experienced angiographer. In case of significant lesion (stenosis or total occlusion), there was an intracoronary nitrates infusion. The severity of coronary stenosis was evaluated by measuring the percent reduction in lumen diameter from a magnified image of the cineangiogram. The Gensini scoring system, and its application to the LAD artery, was used to describe disease extent and complexity (12). In this system, stenosis of the coronary artery lumen was graded as: 1 for 1-25%, 2 for 26-50%, 4 for 51-75%, 8 for 76-90%, 16 for 91-99% stenosis, and 32 for total occlusion. Finally, this score was multiplied by a factor according to the stenotic segment of the related coronary artery. The coronary collateral vessels were graded according to the Rentrop scoring system: 0=no filling; 1=filling of the small side branches; 2=partial filling of the epicardial artery by collateral vessels; 3=complete filling of the epicardial artery

by collateral vessels (13). Patients in Rentrop grades 0, 1, and 2 were classified as Group 1 (inadequate coronary collateral development), and patients in Rentrop grade 3 were classified as Group 2 (adequate coronary collateral development) (14).

### Statistical analysis

Continuous data were expressed as mean ± standard deviation, and categorical data as percentages. SPSS 17.0 (SPSS, Inc., Chicago, Ill, USA) was used to perform statistical procedures. Independent variables were compared via an independent samples t-test, and if there was no normal distribution, via the Mann-Whitney U test. Categorical data were evaluated by a Chi-square test as appropriate. Univariate analysis was used to quantify the association of variables with CC. Variables found to be statistically significant in univariate analysis were used in a multiple logistic regression model with a forward stepwise method in order to determine the independent prognostic factors of adequate CCV. A p value < 0.05 was accepted as significant.

## Results

### Baseline characteristics

The baseline characteristics of patients are summarized in Table 1. There were no significant differences between the two groups in age; presence of hypertension, diabetes mellitus and metabolic syndrome; or level of total cholesterol and LDL, fibrinogen, uric acid, or protein C and S. There were also no significant differences in prior drug use except for statin. Among patients with inadequate CC, hs-CRP levels were significantly higher (p=0.023, Fig. 1), and statin use was significantly lower (p=0.022). The development of coronary collaterals was poor in females (p=0.018).

### Regression analyses for development of adequate CCV

The results of the univariate and multiple logistic regression analyses for development of adequate CC are listed in Table 2. Male gender, prior statin usage, and hs-CRP were found to have prognostic significance in univariate analysis. In a multiple logistic regression model with a forward stepwise method, hs-CRP levels (OR=0.94, 95.0% CI=0.883-1.000, p=0.048), male gender (OR=4.73, 95.0% CI: 1.441-15.539, p=0.010), and statin usage (OR=4.70, 95.0% CI=1.264-17.452, p=0.021) remained associated with the development of CCV after adjustment for variables found to be statistically significant in univariate analysis, and other traditional risk factors (age, hypertension, metabolic syndrome, and diabetes mellitus).

## Discussion

In this study, we aimed to identify possible determinants of coronary collaterals in patients with severe CAD. We found that, hs-CRP levels, male gender, and statin usage were independent predictors of the development of CC.

**Table 1. Baseline characteristics of study patients**

Variables	All patients (n=74)	Coronary collateral circulation		*p
		Inadequate (n=44)	Adequate (n=30)	
<b>Baseline characteristics</b>				
Mean age, years	62±10	63±10	61±10	0.315
Male gender, n (%)	46 (62)	22 (50)	24 (80)	0.018
Hypertension, n (%)	33 (45)	20 (46)	13 (43)	1.000
Diabetes mellitus, n (%)	15 (20)	12 (27)	3 (10)	0.128
Metabolic syndrome, n (%)	30 (41)	21 (48)	9 (30)	0.199
Angina (SAP), n (%)	33 (45)	19 (43)	14 (47)	0.954
<b>Laboratory findings</b>				
hs-CRP, mg/L	12.2±12	14.7±13.5	8.6±9.0	0.023
Protein C, IU/dL	103±28	104±30	101±23	0.690
Protein S, U/dL	86±24	85±27	87±18	0.737
Triglyceride, mg/dL	152±88	159±100	140±66	0.328
Total cholesterol, mg/dL	173±44	171±46	176±41	0.632
HDL, mg/dL	35±9	35±9	34±9	0.457
LDL, mg/dL	109±33	105±31	114±35	0.254
Uric acid, mg/dL	6±2	6±1	6±2	0.805
Fibrinogen, g/L	382±100	395±118	364±64	0.142
<b>Medication</b>				
Antiplatelet agent, n (%)	28 (38)	19 (43)	9 (30)	0.366
ACE inhibitors/ARB, n (%)	30 (41)	20 (46)	10 (33)	0.423
Beta blocker, n (%)	27 (37)	18 (41)	9 (30)	0.477
Statin, n (%)	52 (70)	26 (59)	26 (87)	0.022
Statin usage time, months	4.0±8.5	5.1±9.5	2.4±6.6	0.176
Nitrate, n (%)	8 (11)	6 (14)	2 (7)	0.461
<b>Angiography</b>				
LAD artery stenosis	98±4	96±4	99±2	<0.001
Gensini score	58±30	46±30	75±20	<0.001
LAD Gensini score	51±27	39±24	69±18	<0.001
TIMI II, n (%)	25 (34)	23 (54)	2 (7)	<0.001
Data are presented as number (percentage) and mean±SD values. * Student's t-test and Chi-square test ACE - angiotensin-converting enzyme, ARB - angiotensin receptor blocker, HDL - high-density lipoprotein, hsCRP - high-sensitivity C-reactive protein, LAD - left anterior descending, LDL - low-density lipoprotein cholesterol, SAP - stable angina pectoris				

Despite all the advances in medical and invasive treatment modalities, approximately one in five patients with CAD is unable to have coronary revascularization because of extensive coronary disease and comorbidities. Thus, therapeutic promotion of collateral growth is a valuable treatment strategy for those patients (3).

The importance of coronary collateral developments on several clinical endpoints as positive effects on left ventricle remodeling and reduced infarct size are widely known in

**Table 2. Univariate and multivariate predictors of adequate CCC**

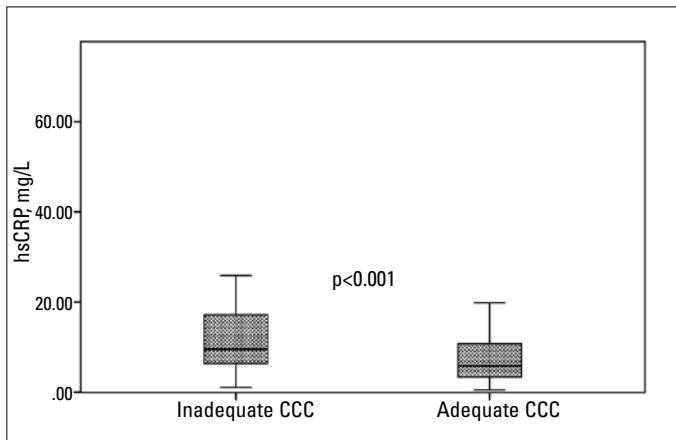
Variables	Univariate			Multivariate		
	OR	p	95% CI	OR	*p	95% CI
<b>Statistically significant variables</b>						
Male gender	4.00	0.011	1.369-11.687	4.73	0.010	1.441-15.539
Statin usage	4.50	0.015	1.339-15.123	4.70	0.021	1.264-17.452
hs-CRP, mg/L	0.95	0.050	0.894-1.000	0.94	0.048	0.883-1.000
<b>Statistically non-significant variables</b>						
Diabetes mellitus	0.29	0.081	0.076-1.160			
Metabolic syndrome	0.47	0.130	0.176-1.250			
Mean age, years	0.98	0.311	0.934-1.022			
Hypertension	0.92	0.857	0.360-2.337			
Angina (SAP)	0.77	1.151	0.453-2.917			
Statin usage time, months	0.95	0.192	0.889-1.024			
Antiplatelet agent	0.56	0.253	0.211-1.506			
ACE inhibitors/ARB	0.60	0.299	0.229-1.573			
Beta blocker	0.62	0.340	0.231-1.568			
Nitrate	0.45	0.353	0.085-2.411			
Protein C, %	0.99	0.685	0.979-1.014			
Protein S, %	1.00	0.750	0.984-1.023			
Triglyceride, mg/dL	0.99	0.361	0.992-1.003			
Total cholesterol, mg/dL	1.00	0.627	0.992-1.013			
HDL, mg/dL	0.98	0.452	0.928-1.034			
LDL, mg/dL	0.99	0.461	0.961-1.018			
Uric acid, mg/dL	1.03	0.789	0.802-1.337			
Fibrinogen, g/L	0.99	0.138	0.991-1.002			
<p>*Multiple logistic regression analysis with forward stepwise method                      Dependent variable - adequate CCC, independent variables: Male gender, statin usage, hs-CRP and other traditional risk factors (age, hypertension, metabolic syndrome, and diabetes mellitus).                      ACE - angiotensin-converting enzyme, ARB - angiotensin receptor blocker, CCC - coronary collateral circulation, CI - confidence interval, HDL - high-density lipoprotein, hs-CRP - high-sensitivity C-reactive protein, LDL - low-density lipoprotein, OR - odds ratio, SAP - stable angina pectoris</p>						

patients with acute myocardial infarction (3-6). However, their effects on overall mortality, possible roles in patients with stable angina, and relations with restenosis followed by percutaneous coronary interventions (PCI) are not clear enough. According to two recent systematic reviews and meta-analyses published by Meier, et al. (15) patients with adequate coronary collaterals had a 36% mortality reduction and less frequent restenosis than patients with inadequate coronary collaterals. The results of these two meta-analyses may suggest that evaluation of coronary collaterals might be useful for risk stratifications in patients with acute myocardial infarction, before PCI, and in patients with stable coronary artery disease (16).

Atherosclerosis is considered to be a chronic inflammatory disease (17). C-reactive protein (CRP) is an indicator of microinflammation. Numerous studies have shown that elevated levels of CRP are associated with increased cardiovascular risk, even in healthy people (18-20). Hs-CRP attenuates nitric oxide production and inhibits angiogenesis, which may result in impaired

collateral development (21). Although in our study coronary angiographic evaluations of patients with a lower level of hs-CRP revealed higher grades of coronary stenosis, no coronary collaterals were observed in patients with higher hs-CRP levels. In multiple analyses, this effect was independent from other factors that influence collateral vessel formation. Comparison of hs-CRP levels in patients with adequate and inadequate coronary collaterals is shown in Figure 1. Although correlations have been reported between hs-CRP and BMI, blood glucose, triglyceride, total cholesterol, and uric acid levels, our study results did not support these findings (22, 23).

Statins are known to reduce ischemic cardiac events by lowering LDL levels, but they may also have immune-modulating and anti-inflammatory properties. The endpoints of primary and secondary prevention studies have shown that, statin use significantly lowers hs-CRP levels in patients with CAD (24-26). In agreement with other investigations, we found that statin therapy is associated with development of collateral circulation (27, 28).



**Figure 1. Comparison of Hs-CRP levels between two groups**

CCC - coronary collateral circulation, hsCRP - high-sensitive C - reactive protein

The development of coronary collaterals is mainly determined by the severity of coronary artery stenosis and the duration of myocardial ischemic symptoms (7, 29). Accordingly, while mean LAD artery stenosis among our study population was  $98 \pm 4\%$ , patients with more severe stenosis had more collateral flow and low TIMI II grade flow ( $p < 0.001$ ). Multivariate analysis of our study results showed that the incidence of coronary collaterals more frequently occurred in males. Our data show that diabetes is not - as shown in an earlier study (30) - an independent predictor for coronary collaterals. Although metabolic syndrome is associated with increased cardiovascular mortality, it is not known if it affects the development of collaterals, and studies are conflicting on this issue (31,32). In our study, there is no relation between coronary collateral circulation and metabolic syndrome. Although many study results have suggested that angiotensin-converting enzyme inhibitors (ACE-I), beta blockers, and nitrates may promote blood vessel growth, clinical study results are generally lacking (33-35). We also did not find any relations between CC and use of this group of drugs.

#### Study limitations:

- The retrospective data evaluation served as limitation.
- The number of patients was not sufficient to show all factors to predict improved coronary collateral development.
- Application of power analysis was not possible.
- Increased blood glucose is a common finding of MS and DM. Additionally, detection of insulin resistance would be meaningful.
- Due to retrospective study design, evaluation of angina duration-which might have a close relation with CC development-was not possible.
- We only performed all measurements at one point in time. Hs-CRP is a sensitive marker for the acute phase of inflammation and has a high within-subject variability. Since we have intended to explore the predictive value of hs-CRP measured at one point in time to detect the relation of the presence of coronary collateral circulation, our study

design reflects routine in daily practice in the majority of cardiology clinics. Further assessment of coronary collateral development by repeated angiographic follow-up would be of interest, but was not performed due to the invasive nature of coronary angiography.

## Conclusion

The presence of coronary collaterals is highly predictable. Among others, demographic and baseline characteristics such as male gender, prior statin usage, and elevated levels of hs-CRP are associated with development of coronary collateralization, and might help to determine their presence. We assume that, randomized clinical studies with follow-up are required to evaluate the role of these possible predictors in long term cardiovascular outcomes.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - C.Z.; Design - C.Z., İ.T.; Supervision - İ.T., E.A.; Resource - İ.T., A.Z.; Materials - C.Z., E.A.; Data Collection&/or Processing - İ.T.; Analysis&/or Interpretation - E.A., A.Z.; Literature Search - C.Z., A.Z.; Writing- E.A., A.Z.; Critical Reviews - E.A., A.Z., C.Z.; Other - İ.T.

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