Influence of clinical characteristics on coronary collaterals

Klinik özelliklerin koroner kollaterallere etkisi

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Abstract

Aim: The presence of coronary collaterals (CC) may exert a protective effect on outcome. Impaired collateral formation could be one of the reasons for increased risks of cardiovascular events. We aimed to determine the influence of clinical characteristics on the presence of CCs in patients with occlusive coronary artery disease.
Materials and methods: This retrospective study enrolled one hundred and fourteen patients who had at least one total occlusion of a coronary artery on angiograms performed between July 2002 and December 2003 at the Department of Cardiology, Pamukkale University. CC flow was graded with Rentrop's classification. Patients were divided in two groups: group 1 with well-developed collaterals and group 2 with less well-developed collaterals.
Results: Demographic, clinical, and laboratory characteristics except the presence of q waves on ECG were similar between the two groups. The presence of q waves in leads V3-4 was associated with poor collateral development (p=0.028). Multivariate analysis determined that estimated glomerular filtration rate (eGFR) was independent predictor of collateral development (p=0.043). Lower eGFR was associated with well-developed collaterals.
Conclusion: In patients with occlusive coronary artery disease, lower eGFR may positively influence the development of CCs. This adaptation may be especially beneficial for patients with lesser degrees of renal dysfunction, who are at greater risk of cardiovascular morbidity and mortality. Treatment modalities that impair the development and function of coronary collaterals should be used cautiously in these patients.

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Key words: Coronary artery disease, coronary collateral circulation, clinical characteristics, renal insufficiency

Özet

Amaç: Koroner kollaterallerin varlığı hastaların klinik sürecinde koruyucu etki yapabilir. Kollateral oluşumunun yetersiz olması kardiyovasküler olayların artışında bir neden olabilir. Bu çalışmada tıkayıcı koroner arter hastalığı olan hastalarda klinik özelliklerin koroner kollateral varlığına etkisini araştırdık.
Gereç ve yöntem: Çalışmaya Temmuz 2002 ve Aralık 2003 yılları arasında Pamukkale Üniversitesi Kardiyoloji Bölümü'nde koroner anjiyografisi yapılan ve en az bir koroner arterinde total oklüzyonu olan hastalar dahil edildi. Çalışmaya retrospektif olarak 114 hasta alındı. Koroner kollateral akım Rentrop sınıflandırması ile derecelendirildi. Hastalar, 1. grup iyi kollateral gelişimi olanlar ve 2. grup daha az kollateral gelişimi olanlar şeklinde iki grupta incelendi.
Bulgular: İki grubun EKG de q dalgaları varlığı dışında demografik, klinik ve laboratuvar özellikleri benzerdi. V3-4 de q dalgalarının varlığı kötü kollateral gelişimi ile ilişkiliydi (p=0.028). Çok değişken analizi yapılarak tahmini glomerüler filtrasyon hızının (tGFH) kollateral gelişiminin bağımsız belirleyicisi olduğu saptandı (p=0.043). Düşük tGFH iyi gelişmiş kollateraller ile ilişkiliydi.
Sonuç: Tıkayıcı koroner arter hastalığı olan hastalarda düşük tGFH koroner kollateral gelişimini pozitif yönde etkileyebilir. Bu adaptasyon, özellikle kardiyovasküler morbidite ve mortalitesi yüksek, düşük düzeyde renal yetmezliği olan hastalar için yararlı olabilir. Bu hastalarda koroner kollateral gelişimini ve fonksiyonunu bozan tedavi yöntemleri daha dikkatli kullanılmalıdır.

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Anahtar Sözcükler: Koroner arter hastalığı, koroner kollateral dolaşım, klinik özellikler, renal yetmezlik

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Introduction

Coronary collaterals (CCs) are anastomatic connections between portions of the same coronary artery and between different coronary arteries [1]. Collaterals exert a protective effect on outcome in a broad spectrum of patients [2]. It is assumed that the presence and absence of CC determine the prognosis of patients with coronary artery disease both during episodes of acute and unexpected ischemia, and during chronic ischemia. The clinical and pathophysiologic determinants of collateral development are not well understood. Cardiovascular risk factors have been suggested to play a role in the development of CCs [3]. However, the mechanism whereby these risk factors may affect collateral development is at present still unknown [4,5]. In addition, studies seeking to determine the influence of cardiovascular risk factors on the presence of the coronary collateral circulation have conflicting results [3,5]. The objective of the study was to determine the influence of clinical characteristics on the presence of CCs in patients with at least one chronic total coronary occlusion.

Materials and methods

The study was carried out retrospectively at the department of cardiology, Pamukkale University, Denizli, Turkey. The study enrolled 114 patients (age, 59 ± 10 years; 84 men, 30 women) who had coronary arteriography for anginal symptoms between July 2002 and December 2003. The study was approved by the institution's Medical Ethics Review Committee. Patients were eligible if they had at least one total occlusion of proximal or mid coronary artery. After coronary arteriography, all patients underwent percutaneous intervention, coronary bypass surgery or medical therapy only at the treating physician's discretion. Exclusion criteria were as follows: (1) a history of past coronary intervention or coronary artery bypass grafting, (2) a serum creatinine level of >2.5 mg/dl. Patient demographic and clinical characteristics included sociodemographic variables (gender, age), anthropometric measurements (waist circumference, body weight and height), medical history (hypertension, diabetes, metabolic syndrome, history of previous MI), social history (smoking, exercise), the presence of chest pain, the presence of family history, the use of medications. Body mass index (BMI) was calculated as weight divided by squared height (kg/m2). Waist circumference was measured at the level of the umbilicus in the late expiration phase. BMI >30 kg/m2 was regarded as obesity. Metabolic syndrome was diagnosed according to the Adult Treatment Panel III Criteria [6]. Fasting venous blood samples were drawn in the morning for fasting blood glucose(FBG), total cholesterol(TCHOL), triglyceride(TG), low density lipoprotein(LDL), high density lipoprotein(HDL), alanin aminotransferase (ALT), aspartate aminotransferase (AST), creatinin (CRT), and complete blood count. Blood glucose levels were measured by UV- photometric measurement. AST, ALT, CRT, TCHOL, TG, LDL, HDL were measured by enzymatic calorimetric measurements in modular 2 (Roche-HITACHI automatic analyzer; serial no: 1706–01) analyzer. Electrocardiograms were obtained for all patients. Echocardiographic images were obtained on all patients using a commercially available system (Contron-Sigma). Data were evaluated retrospectively. eGFR was calculated using Cockcroft and Gault formula (Ccr = [(140-age) x weight (kg)] : [Pcr x 72]). Calculated values were multiplied by 0.85 for women. All patients underwent coronary arteriography for diagnostic purposes. All patients had at least one chronic total occlusion of proximal or mid coronary artery. Collaterals were identified at visual inspection of the baseline angiograms. The Rentrop classification was used to qualify collaterals as follows: 0 = no filling of collateral vessels; 1 = filling of the side branches of the occluded artery without any epicardial filling of the recipient artery; 2 = partial epicardial filling by collateral vessels of the recipient artery; 3 = complete epicardial filling by collateral vessels of the recipient artery. Accordingly, patients were divided in group 1 (well-developed collaterals, Rentrop 2 and 3) and group 2 (less well-developed collaterals, Rentrop 0 and 1). There were 66 patients in group 1 and 48 patients in group 2.

Statistical analysis

Data were analyzed with SPSS (version 10.0; SPSS Inc., Chicago, IL). Continuous variables were compared using the independent-samples t test and categorical variables were compared using the chi-square test or Fisher's exact test. Forward stepwise multiple logistic regression was performed to identify the independent predictors of collateral development, using collateral development as the dependent variable and all patient characteristics significant ($p<0.20$) on univariate analysis as covariates. A $p<0.05$ was regarded as statistically significant.

Results

The mean age of the study population was 59.5 years (range, 35-81). Univariate analysis of patient characteristics in relation to the development of collaterals is shown in Table 1. The use of beta blockers was associated with poor collateral development, albeit not statistically significantly (p=0.114). The presence of q waves in leads V3-4 was significantly associated with poor collaterals (p=0.028). Regional wall motion abnormality (p=0.1), low eGFR (p=0.09), and low HDL levels (p=0.112) were associated with good collateral development, albeit not statistically significantly.

All variables found significant by univariate analysis at p<0.20 were entered into a forward stepwise logistic regression analysis. In addition, clinical factors deemed to be of interest in collateral development were also entered into the analysis. Due to lack of adequate number of HDL measurements, these measurements were not entered into the analysis. Variables, such as eGFR, beta blocker use, the presence of q waves in V3-4, regional wall motion abnormality were entered into logistic regression analysis. Multivariate analysis demonstrated an independent association of eGFR (p=0.043) only with the development of CCs, as shown in Table 2. Lower eGFR was associated with good collateral development.

Table 1. Univariate analysis of baseline and clinical characteristics of the study population (n=114)

Characteristic	All subjects (n=114)	Good collaterals (n=66) Rentrop = 2 and 3	Poor collaterals (n=48) Rentrop = 0 and 1	p values
Age at index angiography, yrs	59.50 ± 9.94	59.66 ± 10.67	59.29 ± 8.94	*0.843*
Male gender, n(%)	84 (73.7)	49 (74.2)	35 (73)	*0.874*
BMI, kg/m^2	29.30 ± 4.31	29.37 ± 4.40	29.20 ± 4.23	*0.832*
Waist circumference, cm	98.41 ± 10.91	98.40 ± 10.22	98.41 ± 11.90	*0.997*
Metabolic Syndrome, n(%)	50 (43.9)	28 (42.4)	22 (45)	*0.887*
Obesity(BMI≥30kg/m2), n(%)	43 (37.7)	27 (40.9)	16 (33.3)	*0.559*
Current smoking, n(%)	42 (36.8)	24 (36.4)	18 (37.5)	*0.901*
Family history, n(%)	28 (24.6)	14 (21.2)	14 (29.2)	*0.330*
Regular exercise, yes, n(%)	12 (10.5)	6 (9.1)	6 (12.5)	*0.558*
Diabetes mellitus, n(%)	46 (40.4)	25 (37.9)	21 (43.8)	*0.528*
Hypertension, n(%)	58 (50.9)	32 (48.5)	26 (54.2)	*0.549*
Statin use, yes, n(%)	17 (14.9)	11 (16.7)	6 (12.5)	*0.537*
ACE-I use, yes, n(%)	23 (20.2)	12 (18.2)	11 (22.9)	*0.534*
Beta-blocker use, yes, n(%)	59 (51.8)	30 (45.5)	29 (60.4)	*0.114*
ASA use, yes, n(%)	73 (64)	41 (62.1)	32 (66.7)	*0.618*
Prior angina pectoris, n(%)	92 (80.7)	55 (83.3)	37 (77.1)	*0.404*
Previous MI, n(%)	55 (48.2)	31 (47)	24 (50)	*0.749*
Laboratory characteristics				
q waves in V3-4	22 (19.6)	8 (12.5)	14 (29.2)	***0.028***
RWMA, n(%)	37 (32.4)	21 (31.8)	17 (35.4)	*0.100*
FPG (mg/dL)	128.20 ± 64.41	126.03 ± 65.79	131.39 ± 63.02	*0.684*
Total Cholesterol (mg/dL)	201.84 ± 57.87	199.92 ± 65.27	204.51 ± 46.30	*0.701*
LDL (mg/dL)	115.42 ± 42.74	115.00 ± 45.17	116.07 ± 39.69	*0.930*
Triglyceride (mg/dL)	163.9 ± 85.5	161.70 ± 122.20	164.17 ± 69.45	*0.908*
HDL (mg/dL)	41.68 ± 10.09	39.93 ± 9.63	44.42 ± 10.43	*0.112*
eGFR (ml/min)	91.61 ± 41.69	85.24 ± 34.89	99.80 ± 48.29	*0.090*

Values are given as percentages or means ± SD. Continuous variables were compared using the independent-samples t test and categorical variables were compared using the chi-square test or Fisher's exact test. BMI: body mass index; ACE-I: angiotensin converting enzyme inhibitor; ASA: acetyl salicylic acid; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; MI: myocardial infarction; RWMA: regional wall motion abnormality.

Table 2. Logistic regression analysis of patient characteristics influencing collateral development

Characteristics	*p value*	odds ratio	*95% CI*
eGFR	**0.043**	1.012	*1.0-1.024*
Beta-blocker use	0.144	0.507	*0.2-1.263*
q waves in V3-4	0.398	0.621	*0.2-1.875*
RWMA	0.704	0.811	*0.27-2.38*

Forward stepwise multiple logistic regression was performed. CI: confidence interval; eGFR: estimated glomerular filtration rate; RWMA: regional wall motion abnormality.

Discussion

In the present study among 114 patients undergoing coronary arteriography for anginal symptoms, we found that lower eGFR has positively influenced the development of CCs. To our best knowledge, this is the first clinical study to show a significant positive correlation between lower eGFR and the presence of CCs. Based on multivariate logistic regression analysis, we found that the association between lower eGFR and the presence of CCs was independent of other patient characteristics. In addition, we found no correlation between the presence of CCs and a number of other patient characteristics including age, myocardial ischemia, obesity, physical exercise, hyperlipidemia, hypertension, diabetes mellitus, and use of various cardiovascular drugs.

The mechanism of the formation of CCs is subject to intense preclinical and clinical research. Previous studies on the relationship between CCs and life-style factors, cardiovascular risk factors, and other patient characteristics have shown conflicting results [3,7].

The stimulation of angiogenesis is the physiological response of a tissue to ischemia [8]. The reason that we observed well-developed CCs in patients with lower eGFR could be more ischemia from accelerated atherosclerosis in renal dysfunction. Special biologic and pathophysiologic factors associated with renal dysfunction, which include dyslipidemia, increased homocysteine, and systemic inflammatory state, may enhance oxidation of LDL-cholesterol and progression of atherosclerotic lesions. In our study, patients with less well-developed collaterals tended to use more beta blockers compared to those with well developed collaterals (p=0.114). Studies in animal models have shown that beta-blockers cause vasoconstriction of coronary collaterals during exercise, thereby diminishing collateral blood flow.

Coronary collaterals may have a protective role in reducing the amount of myocardial cell loss and infarct size [9,10]. In the TIMI trial, infarct size was smaller among patients with collaterals compared to those without collaterals. In this study, patients with less well-developed collaterals had more q waves in leads V3-4 compared to those with well-developed collaterals (p=0.028).

Cardiovascular morbidity and mortality remain as major problems even in patients with mild or moderate degrees of renal insufficiency [11]. Retrospective studies of patients in coronary care units have identified renal dysfunction as the most significant prognostic factor for long term mortality. Also, such studies consistently find renal dysfunction as an independent predictor of death [12]. Several reasons can explain why patients with chronic kidney disease (CKD) have poor outcomes: (1) Excess co-morbidities associated with CKD [13]; (2) Underutilization of proven therapies; (3) Toxicity of therapies; (4) Enhanced vascular pathobiology which include dyslipidemia, increased homocysteine and other thiols, increased inflammatory state, chronic hyperactivation of the sympathetic nervous system, and imbalance between endothelin and nitric oxide [14]. In the present study, we could not detect a relation between cardiovascular risk factors and the presence of coronary collaterals in patients undergoing coronary arteriography for anginal symptoms, as suggested in previous studies [15,16]. Moreover, an inverse association was found between eGFR and CCs. All patients had underutilized proven therapies.

A recent study [17] found a difference in CC vessel formation between uremic and nonuremic patients. They suggested that the endothelial dysfunction underlies the poor collateralization in patients with CKD, which is associated with the increased production of cytokines, low grade inflammation, activation of the renin angiotensin system, and increased oxidative stress. Some other studies [18,19]

also found poor CC in patients with mild to moderate renal dysfunction. They postulated that increased inflammatory activity and impaired endothelial functions could play a role. However, we showed that lower eGFR has positively influenced the CC vessel formation in patients undergoing coronary arteriography for anginal symptoms. This may be due to several reasons. Firstly, we did not exclusively include patients with creatinine levels of ≥1.5 mg/dl only. Rather, we studied patients with higher eGFR compared to those studies. We used the Cockcroft-Goult equation to estimate GFR. Thus, our patients may have a different level of endothelial dysfunction. Secondly, we used coronary arteriography to assess CC, which can only identify vessels >100 μm in diameter. With this technique, intramural collaterals also cannot be demonstrated. It may be possible that patients with mild renal dysfunction have an impaired formation of collateral vessels with a diameter of <100 μm or intramural situated collaterals. Finally, our patients might have a more advanced coronary atherosclerosis. Thus, these patients may already have an impaired endothelial function to such an extent that the influence of renal dysfunction on endothelial dysfunction could be neglected. Collateral vessels as an adaptation to ischemia may be especially beneficial for patients with lesser degrees of renal dysfunction. Beta-blockers may induce vasoconstriction of coronary collaterals, reducing blood flow to collateral-dependent myocardium during episodes of ischemia. Thus, beta-blockers should be used cautiously in renal dysfunction in the absence of coronary artery disease, heart failure, post-myocardial infarction, high coronary disease risk, diabetes, and tachyarrhythmias. Drug-eluting stents (DES) may impair the development and function of coronary collaterals [20]. They also could impair collateral protection in the case of stent thrombosis. In addition, the effect of DES in decreasing the need for repeat revascularization is attenuated in patients with renal dysfunction [21].

Several aspects of the present study should be mentioned. We determined the presence or absence of CC circulation, but not the development of collaterals over time. We used coronary angiography to assess CC, which can only identify vessels >100 μm in diameter, whereas most collateral vessels are smaller [22]. The quantitative indices of collateral circulation were better markers of the functional significance of CC. In this regard, a superior technique by intracoronary pressure and/or flow velocity assessments can be performed. But, this can only be performed during angioplasty, which restricts its applicability to a limited population.

We conclude that there is no significant association between cardiovascular risk factors and the presence of CCs. However, we showed that lower eGFR is associated with well-developed CCs. This adaptation may provide an alternative source of blood supply to jeopardized myocardium in patients with lesser degrees of renal dysfunction. New therapeutic interventions toward improving coronary collateral development at this stage of renal dysfunction before further impairment of endothelial function may be a promising strategy in treatment of such patients. DESs should be cautiously used in these patients because they could impair the development and function of CCs.

Conflict of interest: None.

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