Predictors of poor coronary collateral development in patients with stable coronary artery disease: Neutrophil-to-lymphocyte ratio and platelets

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Abstract

Objective: The heterogeneity in the degree of collateralization among patients with coronary artery disease (CAD) remains incompletely understood. We evaluated the predictors of poorly developed coronary collateral circulation (CCC) in patients with stable coronary artery disease.
Methods: Current study is a retrospective study, consisting of 118 patients with poor CCC and 130 patients with good CCC. We investigated predictors of poor coronary collaterals in a cohort of 248 patients who had high-grade coronary stenosis or occlusion on their angiograms. To classify CCC, we used the Rentrop classification.
Results: Patients with poorly developed CCC had significantly higher neutrophil-to-lymphocyte ratio (N/L) compared with those with well-developed CCC, (4.2±2.8 vs. 3±3.1, p=0.001), whereas mean platelet volume, red cell distribution width and uric acid were not significantly different. Logistic regression analysis showed that N/L ratio (odds ratio 1.199, 95% confidence interval 1.045-1.375) and serum triglyceride levels [odds ratio (OR)=1.006, 95% confidence interval (CI)=1.001-1.010] were independent predictors of poorly developed CCC.
Conclusion: An elevated level of N/L ratio is independently associated with a significant impairment in coronary collateralization. Our findings suggest that N/L ratio is an inexpensive, universally available hematological marker for sufficiency of CCC in patients with stable coronary artery disease. *(Anatol J Cardiol 2015; 15: 218-23)*
Keywords: coronary collateral circulation; neutrophil to lymphocyte ratio, uric acid; hematologic parameters

Introduction

The development of coronary collaterals is an adaptive response to chronic myocardial ischemia and protecting from tissue damage and infarction (1). These vessels provide an alternative source of blood supply to the myocardium in patients with occlusive coronary lesions. Increase in coronary collateral blood flow may reduce angina symptoms and cardiovascular events and preserve contractile function (2). Patients with coronary stenosis or occlusion develop varying degrees of collateral formation despite similar degrees of coronary obstruction. Although severity of coronary stenosis (3), presence of diabetes mellitus (4), levels of inflammatory cells (5), and certain growth factors such as vascular endothelial growth factor (6), and angiopoietin (7), were all suggested as potential determinants of collateral development, the mechanisms for the different individual ability to develop collateral circulation are still unclear.

The inflammatory process plays an important role at all stages of coronary artery disease (CAD) (8). White blood cell (WBC) subtypes, especially the neutrophil-to-lymphocyte ratio (N/L ratio), can be used as an indicator of systemic inflammation. In the present study, we examined the relation between, N/L ratio as an established marker of systemic inflammation and the development of CCC as evaluated by coronary angiography in patients with chronic stable angina pectoris. Furthermore, we hypothesized that increasing levels of mean platelet volume (MPV), red cell distribution width (RDW) and uric acid would also be inversely associated with presence of coronary collaterals.

Methods

Study design

Our study is an observational case-control study, patients were selected from patients who had poor coronary collateral circulation (poor CCC group) and controls were selected from patients who had good coronary collateral circulation (control group).

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Study population

A total of 118 consecutive patients with good coronary collateral circulation and 130 age and gender-matched subjects with poor coronary collateral circulation were retrospectively investigated. Patients were included in the present study after the following exclusions: patients with coronary artery lumen diameter stenosis <90% (n=990), recent history (i.e. a history of less than one month) of acute coronary syndrome (n=580), valvular heart disease (n=155), congestive heart failure (n=290), renal dysfunction (creatinine >1.5 mg/dL) (n=457), anemia (n=270), hepatic and hemolytic disorders (n=51), concomitant inflammatory diseases and neoplastic diseases (n=88). Patients taking steroids, immunosuppressive drugs or nonsteroidal anti-inflammatory drugs except for low-dose aspirin were also excluded from the study (n=78). All patients were selected from 2932 individuals who underwent elective coronary angiography, on suspicion of coronary artery disease, during a 4-year period from January 2009 to January 2013. Detailed physical examination and an electrocardiographic and echocardiographic evaluation were performed on all patients. The local Ethical Committee approved the study protocol.

Definitions

Hypertension was defined as blood pressure 140/90 mm Hg or greater, or if they had a history of antihypertensive drug use (9). Diabetes mellitus (DM) was defined as fasting blood glucose≥126 mg/dL on two occasions or being on treatment (10). Dyslipidemia was defined as serum total cholesterol ≥240 mg/dL, serum triglyceride ≥200 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, high-density lipoprotein cholesterol <35 mg/dL, or taking any lipid-lowering medication (11). Current smokers were defined as having a history of smoking for a certain period within the past year. Admission anemia was defined as a baseline hemoglobin (Hb) concentration less than 13 mg/dL in men and less than 12 mg/dL in women (12).

Coronary angiographic analysis

Coronary angiography was commonly indicated because of clinical symptoms or results of noninvasive tests that suggested myocardial ischemia. Coronary angiography was performed using the standard Judkins technique. The angiographic characteristics, which included grade of coronary collateral circulation and percentage stenosis of all coronary lesions in the index coronary angiogram were obtained from reviewing the angiogram using a quantitative coronary angiographic system. Two experienced cardiologists blinded to the study protocol carried out the angiographic analysis. The coronary collateral circulation was graded using the Rentrop classification (13): grade 0=no filling of any collateral vessel; grade 1=filling of side branches of the artery to be the epicardial segment; grade 2=partial filling of the epicardial artery by collateral vessels; and grade 3=complete filling of the epicardial artery by a collateral vessel. Patients were then divided into three groups according to their collateral grades. The 'poor collateral group' comprised patients with at least one vessel having ≥90% stenosis and grade-0 or grade-1 collaterals. The 'good collateral group' consisted of patients with at least one vessel having ≥90% stenosis and grade-2 or grade-3 collaterals. In patients with more than 1 collateral vessel filling the occluded vessel, the collateral vessel with the highest Rentrop grade was used for analysis.

Laboratory measurements

A fasting venous blood sample was obtained in the morning before coronary angiography. Levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in serum were measured using an Abbott Aeroset auto analyzer-with original kits (Abbott Laboratories. Abbott Park, Illinois, U.S.A). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation. Serum uric acid levels were measured using an enzymatic colorimetric test on a Roche/Hitachi analyzer. Hemoglobin, and other hematologic paramaters were measured on Cell-Dyne counter of Abbott Laboratories (Cell-dyne 3700 Abbott Laboratories, IL, USA). The N/L ratio was obtained by dividing total count of neutrophils by lymphocytes count.

Statistical analysis

All analyses were performed using SPSS V 16.0 for Windows (version 16.0, SPSS, Chicago, Illinois). All data are presented as mean±standard deviation unless otherwise stated. Comparison of parametric values between the 2 groups was performed by means of independent samples t test. Categorical variables were compared by the chi-square test. Spearman correlation coefficient was computed to examine the association between 2 continuous variables.

Univariate logistic regression models were first performed to evaluate the crude association between the development of adequate CCC and each of the factors-including age, sex, serum HDL cholesterol, LDL cholesterol, serum triglycerides, creatinine, cigarette smoking, diabetes, hypertension, uric acid, MPV, RDW, and N/L ratio individually. Those factors that were significant at the p≤0.10 level in the univariate models were put into the multiple logistic regression models to identify the factors that were independently associated with the presence of subclinical coronary atherosclerosis. A receiver-operating characteristic (ROC) curve was constructed. All statistical tests were two-sided, and statistical significance was determined at a p value <0.05.

Results

A total of 248 patients with chronic stable angina pectoris were enrolled. In all of the studied patients, the mean age was 64.3±10 years and 32.9% of the patients were female. Among 118 patients with good coronary collateral circulation, 44 patients had Rentrop grades 3 and 74 patients had Rentrop grades 2. Among 130 patients with poor coronary collateral circulation, 38 patients had Rentrop grades 1 and 92 patients had no coronary collaterals.

Table 1. Baseline clinical and laboratory characteristics of poor CCC and control groups

	Poor CCC	Good CCC	*P*
Age, years	64.3±9.6	64.4±10.5	0.888
Male gender, n (%)	90 (69.2)	83 (70.3)	0.798
Hypertension, n (%)	46 (35.3)	32 (27.1)	0.223
Diabetes, n (%)	38 (29.2)	27 (22.8)	0.254
Dyslipidemia, n (%)	27 (20.7)	21 (17.7)	0.563
Smoking, n (%)	9 (6.9)	19 (16.1)	**0.026**
Hemoglobin, g/dL	13.7±1.8	13.2±1.7	**0.025**
MPV, fL	8.7±1.1	8.8±1.1	0.430
PDW, %	16.6±0.7	16.3±0.6	0.120
RDW, %	14.6±1.2	14.8±2.2	0.251
Neutrophil count, 109/L	5.3 ±2.1	5.0±1.9	0.101
N/L ratio	4.2±2.8	3±3.1	**0.001**
White blood cell, count, 109/L	8±2.8	8.3±2	0.328
LDL cholesterol, mmol/L	110±33	113±53	0.662
HDL cholesterol, mmol/L	45.3±13.9	47.1±12.9	0.429
Triglyceride, mmol/L	185.1±105	146.9±88	**0.009**
Uric acid, mg/dL	5.1±1.7	5±2.2	0.933
Creatinine, mg/dL	1±0.6	1±0.5	0.892
Left ventricular EF (%)	56.9 (7)	57.7 (7.4)	0.487
Beta-blocker use, n (%)	29 (22.3)	28 (23.7)	0.696
ACE inhibitor use, n (%)	23 (17.6)	24 (20.3)	0.428
Statin use, n (%)	18 (13.8)	16 (13.5)	0.860
Nitrates, n (%)	17 (13.3)	16 (13.5)	0.872
Calcium canal blokers, n (%)	18 (13.8)	15 (13.1)	0.796

CCC - coronary collateral circulation; EF - ejection fraction; HDL - high density lipoprotein; LDL - low-density lipoprotein; N/L ratio - neutrophil/lymphocyte ratio; PDW - platelet distribution width; RDW - red cell distribution width. In bold are significant.

Demographic and clinical patient characteristics are listed in Table 1. Age, presence of hypertension and diabetes mellitus, dyslipidemia, lipid profiles including LDL to HDL cholesterol, uric acid, left ventricular ejection fraction and baseline medications were not different between the good CCC and poor CCC groups. Also, MPV, RDW, WBC, and platelet distribution width (PDW) were not different among the study groups. The frequency of smoking was higher in the good CCC group than the poor CCC group. Serum triglyceride (185.1±105 vs. 146.9±88 mg/dL, p=0.009), hemoglobin (13.7±1.8 vs. 13.2±1.7 g/dL, p=0.025), and N/L ratio (4.2±2.8 vs. 3±3.1, p=0.001) were significantly higher in the poor CCC group than in the good CCC group (Table 1). In all subjects, the N/L ratio was negatively correlated with Rentrop score (r=-0.203; p=0.001).

By univariate logistic regression analyses, risk factors associated with the development of adequate CCC at the p<0.05 level included smoking, serum trigliserid, hemoglobin and N/L ratio (Table 2). After adjusting for all covariates, poor CCC was associated with serum trigliserid [odds ratio (OR)=1.006, 95% confidence interval (CI)=1.001-1.010, p=0.017] and N/L ratio [odds ratio (OR)=1.199, 95% confidence interval (CI)=1.045-1.375, p=0.009]. The ROC analysis provided a cut-off value of 2.55 for N/L ratio to predict poor CCC with 76% sensitivity and 63% specificity, with the area under the ROC curve being 0.735 (95% CI 0.672-0.798, p<001, Fig. 1).

Table 2. Univariate and multivariate analyses of poorly developed coronary collateral circulation

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	***P***	**OR**	**95%CI**	***P***
Age	0.998	0.975-1.012	0.887			
Gender	0.907	0.525-1.562	0.735			
Hypertension	0.712	0.420-1.180	0.194			
Diabetes mellitus	0.885	0.530-1.468	0.633			
Smoking	0.426	0.199-0.926	0.028	0.677	0.227-2.023	0.485
HDL	0.991	0.970-1.014	0.427			
LDL	0.999	0.990-1.008	0.660			
Triglyceride	1.005	0.992-1.013	0.016	1.006	1.001-1.010	0.017
Uric acid	1.007	0.865-1.241	0.933			
Creatinine	1.030	0.670-1.526	0.891			
Hemoglobin	1.167	1.018-1.320	0.029	1.210	1.006-1421	0.054
N/L ratio	1.213	1.065-1.381	0.004	1.199	1.045-1.375	0.009
MPV	0.919	0.745-1136	0.429			
RDW	0.919	0.790-1061	0.253			

CI - confidence interval; HDL - high-density lipoprotein; LDL - low-density lipoprotein, MPV - mean platelet volume N/L ratio-neutrophil/lymphocyte ratio; OR - odds ratio; RDW - red cell distribution width
Univariate and multivariate regression analysis

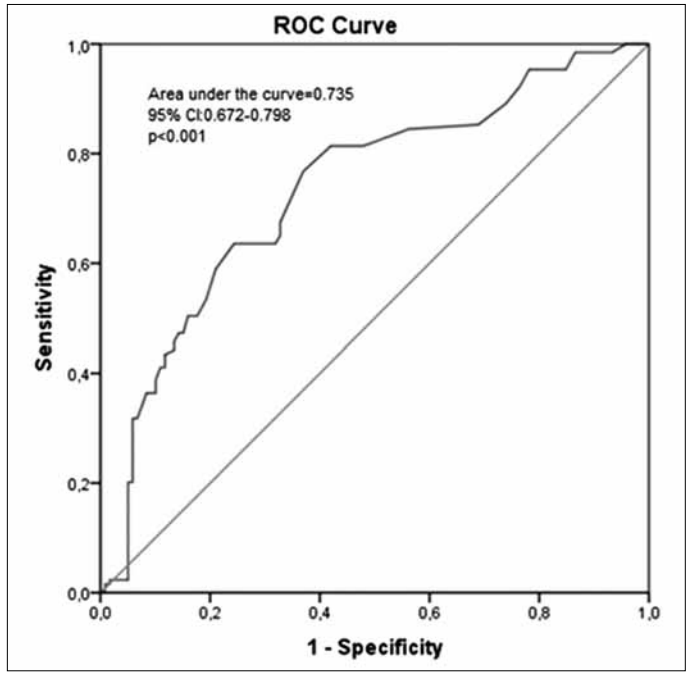

Figure 1. Receiver-operating characteristic curve analysis for neutrophil-to-lymphocyte ratio for prediction of poor collateral

Discussion

Our findings indicated that elevated N/L ratio was associated with a significant impairment in coronary collateralization.

The presence of good collateral circulation has beneficial effects on ventricular function, infarct size, and aneurysm formation (14). A meta-analysis of 12 studies showed that patients with good collateralization have 36% reduced mortality risk compared with patients with low collateralization (15). Therapeutic promotion of collateral growth is a valuable treatment strategy in patients who cannot be revascularized by percutaneous coronary intervention or coronary artery bypass grafting. It is important to define the determinants of CCC development by further studying CCC and its mechanisms.

The inflammatory process plays a major role at all stages of atherosclerosis from initiation through progression and in the thrombotic complications of this disease (16). Although different inflammatory cells including neutrophils, eosinophils, and monocytes have been related to development of CAD, the N/L ratio is a combination of 2 independent markers of inflammation. Neutrophils secrete large amounts of inflammatory mediators and elevated neutrophil count is independently associated with long-term mortality in patients with myocardial infarction (17). In contrast, relatively low lymphocyte counts reflect a physiologic stress response to cortisol and are independently associated with worse prognosis in patients with CAD (18). Therefore, the ratio between the absolute number of neutrophils and the number of lymphocytes provides a simple method for assessment of the inflammatory status and prognosis in patients with coronary artery disease. The association between the N/L ratio and severity of coronary atherosclerosis has been reported in patients with ischemic heart disease (19). In the present study, N/L ratio was found to be an independent predictor of the coronary collateral circulation development in patients with stable coronary artery disease.

There is significant evidence that the collateral circulation development occurs as a result of angiogenesis and/or arteriogenesis (20). CRP as an indicator of inflammation inhibits the production of nitric oxide (NO), and diminishes NO bioactivity, thus, inhibits angiogenesis (21). A recent study by Schneeweis et al. (22) showed that chronic inflammation inhibits Akt phosphorylation and endothelial cell (EC) migration. Long-term exposure to inflammation also inhibits vascular endothelial growth factor (VEGF)-induced EC migration (23). Fichtlscherer et al. (24) showed that elevated CRP serum levels indicative of a systemic inflammatory response are associated with a profound impairment in systemic endothelial vascular reactivity in patients with coronary artery disease. Chronic inflammation also inhibits endothelial progenitor cell differentiation, survival, and function, key components of angiogenesis and the response to chronic ischemia, which supports the role of inflammation in angiogenesis (25). It has also been shown that chronic inflammation induces endothelial cell apoptosis and production of proinflammatory mediators in human mononuclear cells (26).

Several studies have found that poorly developed collateral circulation in coronary artery disease was related to chronic inflammation of low degree, as evidenced by high levels of CRP (27-29). Moreover, Güleç et al. (30) reported an association between poor coronary collateral circulation and elevated concentrations of high-sensitive CRP in patients who predominantly had acute coronary syndromes. It has been reported that detectable serum TNFα concentrations were measured significantly more often in patients with insufficient collaterals than in those with sufficient collaterals, and that TNFα as an indicator of inflammation was inversely related to simultaneously measured coronary collateral flow (31). Güray et al. (32) demonstrated that in patients with obstructive CAD, poor collateral circulation is associated with higher levels of soluble endothelial adhesion molecules (CAMs) including vascular cell adhesion molecule (VCAM-1) intercellular adhesion molecule-1 (ICAM-1) and E-selectin. Statin therapy has been shown to be associated with better coronary collateral development (29, 33). In our study statin usage was not different between the poor CCC and good CCC groups. Recently, high serum leucocytes were found to be associated with poorly developed collaterals (34). In this study, we consistently found high N/L ratio in patients with poorly developed CCC.

Endothelial dysfunction may also explain poor collateral development, as the endothelium is an important factor in collateral development. Elevated CRP serum levels indicative of a systemic inflammatory response have been found to be associated with endothelial dysfunction (24). NO is the key endothelium-derived relaxing factor that plays a pivotal role in the maintenance of vascular tonus and in the collateral-enhancing effect of vascular endothelial growth factor (35). It has been reported that CRP as an indicator of inflammation induces the expression of proinflammatory proteins in endothelial cells and downregulates endothelial NO synthase (eNOS) protein levels (21, 36). Impaired collateral development in patients with elevated CRP levels might be explained through a direct effect on decreasing NO production and CRP-mediated endothelial dysfunction.

Serum uric acid (SUA) has been proposed as a biomarker for sufficiency of CCC but the association between SUA levels and development of CCC is controversial. Several studies have shown an inverse relationship between SUA and the presence of coronary collaterals (37, 38). By contrast, SUA levels were not associated with development of CCC in two recent studies (27, 39). It was also shown that hematologic parameters such as, MPV and RDW are significantly associated with the development of CCC (40, 41). However, in our cohort MPV, RDW and SUA levels were not different between the poor CCC and good CCC groups. Kadı et al. (42). reported that HDL-C is positively correlated with CCC. In our study, among lipid indices, triglyceride, but not HDL-C, was associated with CCC. Smoking has been linked to coronary collateral circulation previously in patients with ischemic heart disease (43). Mildly decreased GFR has also been found to be associated with poor collateral circulation development (44). In the present study, smoking and serum creatinine levels were similar between patients with poor and good CCC.

Study limitations

This study has several limitations. First, the sample size in our study was relatively small. A single measurement of N/L ratio may not reflect lifetime status, and coronary collateralization progresses over many years. In this study, the patients did not undergo IVUS (intravascular ultrasonography) to measure coronary collateralisation. The gold standard for measuring collateralisation is intravascular haemodynamic assessment (coronary flow index). However, invasiveness of intravascular ultrasonography limits its use in large-scale studies. Also, the Rentrop scoring system was used for collateral grading even though small microvascular caliber vessels may not be visualized angiographically. In addition, we could not study the other inflammatory markers such as serum CRP, fibrinogen, and interleukins. Finally, although we speculate that endothelial dysfunction may be a mechanistic link between increased N/L ratio and adverse outcomes in this population, we did not assess oxidative markers, cytokines, and pro-arteriogenic markers. If these had been studied in our study, they might have provided much more informative data on the role of endothelial dysfunction and angiogenesis in the etiopathogenesis of CCC.

Conclusion

This study showed that, in patients with stable coronary artery disease, elevated N/L ratio levels as an indicator of inflammation are independently associated with a significant impairment in coronary collateralization; and patients with poorly developed collaterals tend to have a higher N/L ratio. Our data suggest that N/L ratio may be simple, reliable, and economical marker of coronary collateral circulation. Our findings provide impetus for additional studies to address the underlying mechanism and treatment.

Conflict of interest: None declared.

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