

Relation of C-Reactive Protein to Coronary Collaterals in Patients With Stable Angina Pectoris and Coronary Artery Disease

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The heterogeneity in the degree of collateralization among patients with coronary artery disease (CAD) is poorly understood. We sought to determine whether chronic subclinical inflammation is related to coronary collateral development in patients with chronic stable angina pectoris and obstructive CAD. High-sensitivity C-reactive protein (CRP) levels were measured in 177 patients with stable angina pectoris before coronary angiography. Multi-variable logistic regression revealed an inverse graded association between CRP and the presence of coronary collaterals (Rentrop grade 1 to 3). Compared with patients in the first CRP tertile, the adjusted odds ratio for the presence of coronary collaterals was 0.70 (95% confidence interval, 0.33 to 1.52; $p = 0.45$) for patients in the second CRP tertile and 0.33 (95% confidence interval, 0.15 to 0.75; $p = 0.008$) for patients in the third CRP tertile (p for trend = 0.008). In conclusion, an inverse graded association exists between CRP and the presence of coronary collaterals in patients with stable angina pectoris. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:509–512)

There is marked heterogeneity in the degree of coronary collateral development among patients with coronary artery disease (CAD). Although some clinical parameters, such as the anatomic extent of disease, are somewhat predictive of the ability to develop angiographically visible collaterals, much of the variability in the degree of coronary collateralization remains poorly understood.¹ Inflammation has emerged as central to the initiation and progression of atherosclerosis. A complex interaction exists between new blood vessel formation and inflammation.² However, little data are available on the relation between inflammation and the development of coronary collaterals.^{3,4} In the present study, we examined the relation between C-reactive protein (CRP), an established marker of systemic inflammation and the development of collateral vessels as evaluated by coronary angiography in patients with chronic stable angina pectoris.

Methods and Results

The patients included in this study were prospectively selected from a total of 3,021 consecutive patients who were referred for coronary angiography at our institution between November 2004 and April 2006. Inclusion criteria were stable angina pectoris with a stenosis of $\geq 90\%$ in ≥ 1 coronary vessel. Exclusion criteria included (1) any known inflammatory, neoplastic or infectious disease, (2) treatment with steroids, immunosuppressive drugs or nonsteroidal anti-inflammatory drugs except for low-dose aspirin, (3) acute

coronary syndrome within the previous month, (4) coronary angiography with or without intervention within the previous month, and (5) history of coronary artery bypass operation. The hospital investigational review committee approved the study protocol, and informed written consent was obtained from each patient.

Coronary angiography was performed using standard techniques. Images were acquired at optimal projection angles and digitally recorded on a Coroskop Plus with the Hicor TOP digital system (Siemens AZ, Erlangen, Germany). Coronary angiograms were assessed using an off-line system (Pie Medical Imaging, Maastricht, The Netherlands). Disease severity was assessed by determining the number of vessels with $>70\%$ stenosis.

The presence of coronary collaterals was assessed using the Rentrop grading system⁵ as follows: 0 = no filling by contrast dye of the distal vessel via collaterals, 1 = filling of small side branches only, 2 = major side branches of the main vessel filled, and 3 = main epicardial vessels filled by collaterals. In subjects with >1 collateral supplying the distal aspect of a diseased artery, the higher collateral score was used. In patients with >1 qualifying severely diseased vessel, the vessel with the higher collateral score was chosen for analysis. Grades 1 to 3 were defined as the presence of collateral circulation.

The degree of collaterals was assessed in a blinded manner by 2 experienced interventional cardiologists (AK, LG) without knowledge of the clinical data or CRP levels. The reproducibility of the Rentrop score was high (Cohen's $\kappa = 0.87$, 95% confidence interval 0.76 to 0.91). When there was a disagreement, the difference was adjusted by a third investigator.

Blood samples were obtained immediately before angiography. High-sensitivity CRP was measured with latex-enhanced immunonephelometry (Dade Behring, Marburg, Germany) as previously described.⁶

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Table 1
Baseline clinical characteristics and angiographic findings

Variable	Coronary Collaterals		p Value
	No (n = 87)	Yes (n = 90)	
Age (yrs)	59 (52, 67)	61 (54, 68)	0.40
Men	77 (89%)	79 (88%)	0.88
Smoker			
Past	29 (33%)	23 (26%)	0.26
Current	8 (9%)	13 (14%)	0.28
Diabetes mellitus	32 (37%)	24 (27%)	0.15
Dyslipidemia [†]	74 (85%)	74 (82%)	0.82
Hypertension*	55 (63%)	60 (67%)	0.63
Body mass index (kg/m ²)	29 (25, 32)	29 (26, 32)	0.70
Serum creatinine (mg/dl)	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.49
Medications at study entry			
Aspirin	68 (78%)	72 (80%)	0.76
Angiotensin-converting enzyme inhibitors	48 (55%)	43 (48%)	0.33
β blockers	46 (53%)	58 (64%)	0.12
Statin	58 (67%)	58 (64%)	0.76
Multivessel disease	28 (39%)	35 (43%)	0.68
Previous infarction	31 (36%)	39 (43%)	0.30
Previous percutaneous coronary intervention	45 (52%)	45 (50%)	0.82

Data are expressed as median (interquartile range) or number (percent) for categorical variables.

* Blood pressure \geq 140/90 mm Hg or use of antihypertensive medication.

[†] Total cholesterol $>$ 200 mg/dl or use of lipid-lowering medication.

Continuous variables are presented as medians (with interquartile ranges) and categorical variables as numbers and percentages. Comparisons among groups were tested with the Mann-Whitney U test for continuous variables and by the chi-squared statistic for noncontinuous variables. The relation between median CRP levels across Rentrop grades was assessed using the nonparametric Jonckheere-Terpstra test.

Univariable and multivariable logistic regression analyses were performed to determine the relation between clinical and laboratory parameters and the presence of any coronary collaterals (Rentrop score 1 to 3). The following baseline clinical characteristics were considered in the multivariable procedure: age, gender, history of diabetes, history of hypertension, smoking status, the number of diseased vessels, previous infarction, and use of statins before the procedure. CRP was modeled as an indicator variable with the odds ratio (OR) for the presence of coronary collaterals of patients in the second and third CRP tertile compared with that of patients in the first CRP tertile. A secondary analysis was performed using CRP cutoffs for low- ($<$ 1 mg/L), medium- (1 to 3 mg/L), and high-risk CRP levels ($>$ 3.0 mg/L).⁷ Differences were considered statistically significant at the 2-sided $p <$ 0.05 level. All statistical analyses were performed using SPSS statistical software (version 12.0, SPSS, Inc., Chicago, Illinois).

A total of 177 patients with chronic stable angina pectoris were enrolled. Coronary collaterals were present in 90 patients (50.8%), with 26 (14.7%), 42 (23.7%), and 22 (12.4%) patients having Rentrop grades 1, 2, and 3, respec-

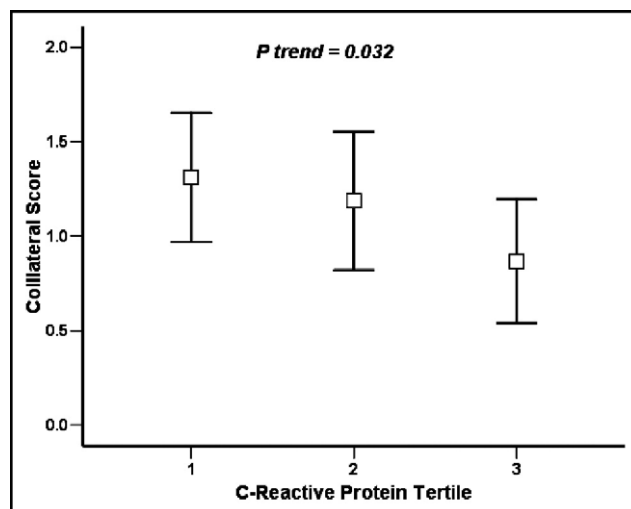


Figure 1. Mean and 95% confidence intervals of the collateral score according to tertiles of CRP.

tively. The clinical characteristics of the study sample are presented in Table 1.

Median CRP levels were significantly lower among patients with coronary collaterals than among patients without (2.4 mg/L [interquartile range 1.0 to 4.6] vs 3.9 mg/L interquartile range 1.8 to 5.9]; Mann-Whitney $p = 0.028$). An inverse stepwise association was present between collateral score and tertiles of CRP (Figure 1). CRP levels decreased with increasing Rentrop grade, with median CRP levels of 3.9, 2.8, 2.0, and 2.7 mg/L in patients with Rentrop grades of 0, 1, 2, and 3, respectively (p for trend = 0.043).

Univariable logistic regression revealed an inverse graded association between CRP levels and the presence of coronary collaterals (Table 2). In a multivariable logistic regression model, CRP remained a significant independent predictor of the presence of coronary collaterals (Table 2, model 1). Analyzing only patients with previous myocardial infarction ($n = 70$) gave similar results. Compared with patients in the first CRP tertile, the adjusted ORs for the presence of coronary collaterals was 0.29 (95% confidence interval 0.07 to 1.10; $p = 0.07$) for patients in the second CRP tertile and 0.14 (95% confidence interval 0.03 to 0.60; $p = 0.009$) for patients in the third CRP tertile.

The inverse association between CRP levels and the presence of coronary collaterals was also present when the patients were categorized according to the American Heart Association cutoffs for CRP levels (Table 2, model 2). Finally, we used CRP as a continuous variable in the model (after logarithmic transformation). For each unit increase of CRP, the OR for the presence of coronary collateral decreased to 0.72 (95% confidence interval 0.53 to 0.97, $p = 0.029$). There were no discernible differences in the results when only patients with CRP values $<$ 10 mg/L ($n = 157$) were analyzed (data not shown).

Discussion

The results of the present prospective study demonstrate a graded inverse independent association between CRP levels and collateral development in patients with chronic stable

Table 2
Multivariable logistic regression for the presence of coronary collaterals according to CRP levels*

	n	Collaterals	Unadjusted			Adjusted		
			OR (95% CI)	p Value	p Value for Trend	OR (95% CI)	p Value	p Value for Trend
Model 1	177							
First CRP tertile (<1.8 mg/L)	58	35 (60%)	1.0		0.017	1.0		0.008
Second CRP tertile (1.8–4.5 mg/L)	59	32 (54%)	0.78 (0.37–1.62)	0.50		0.70 (0.33–1.52)	0.45	
Third CRP tertile (>4.5 mg/L)	60	23 (38%)	0.41 (0.20–0.86)	0.018		0.33 (0.15–0.75)	0.008	
Model 2	177							
Low risk (CRP <1 mg/L)	32	21 (66%)	1.0		0.019	1.0		0.007
Medium risk (CRP 1–3 mg/L)	56	31 (55%)	0.65 (0.26–1.60)	0.35		0.64 (0.25–1.63)	0.34	
High risk (CRP >3 mg/L)	89	38 (43%)	0.39 (0.17–0.91)	0.029		0.32 (0.13–0.78)	0.013	

* The final model adjusted for age, gender, body mass index, history of hypertension and diabetes, current smoking, number of diseased vessels, previous infarction, and statin therapy.

CI = confidence interval.

angina pectoris. These findings are consistent with several recent reports. Seiler et al⁸ demonstrated that tumor necrosis factor- α was detectable more often in patients with insufficient collaterals compared with those with sufficient collaterals. Guray et al⁹ reported an association between poor coronary collateral circulation and elevated concentrations of soluble adhesion molecules, a marker of cytokine-induced endothelial activation. Finally, Gulec et al⁴ reported that elevated CRP levels were associated with an impairment in coronary collateralization in patients who predominantly had acute coronary syndromes.

In patients with previous myocardial infarction, myocardial segments with normal regional function may have better collateral support compared with segments with impaired regional function. However, the inverse association between CRP and coronary collaterals was also present in the subgroup of patients with previous infarction.

In patients with stable angina pectoris, elevated CRP is associated with increased risk of death and myocardial infarction.¹⁰ This association cannot be explained by a greater degree of atherosclerotic burden, because there is poor correlation between CRP and CAD severity.¹¹ Beyond the prediction of cardiovascular events, elevated CRP is also a strong predictor of exercise-induced ischemia in patients with CAD.¹² Thus, a possible explanation for the association between CRP and exercise-induced ischemia is that patients with elevated CRP may have less collateral support.

The variable presence of collateral circulation on coronary angiograms among patients with CAD is poorly understood.¹ Reports relating metabolic disorders such as diabetes^{13,14} and the metabolic syndrome^{15,16} to impaired collateral development have been inconsistent. Interestingly, CRP levels are elevated in diabetes and the metabolic syndrome.^{6,17} The results of the present study suggest that the accompanying subclinical inflammation rather than the metabolic disorder may be the dominant characteristic leading to impaired collateral development.

Our study cannot provide a mechanism for the association between subclinical inflammation and reduced collaterals in patients with stable angina. CRP decreases nitric oxide production, which, in turn, inhibits angiogenesis.¹⁸ Statins, which

reduce CRP levels, have been shown to promote angiogenesis.¹⁹ Diseases that produce systemic inflammation are associated with a depletion of circulating endothelial progenitor cells,²⁰ which participate in collateral development.

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