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Article *in* Acta Cardiologica Sinica · December 2012

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Coronary Artery Disease

Relationship between Leukocyte and Subtype Counts, Low-Grade Inflammation and Slow Coronary Flow Phenomenon in Patients with Angiographically Normal Coronary Arteries

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Background: Slow coronary flow (SCF) is an angiographic finding characterized by delayed opacification of epicardial coronary arteries in the absence of obstructive coronary disease. Leukocytes and low-grade inflammation play a major role in atherosclerotic vascular processes and may be important in other coronary pathologies. Therefore, we aimed to investigate whether there is a positive correlation between leukocyte counts, high-sensitive C-reactive protein (hsCRP) and SCF determined by frame rates.

Methods: Seventy-seven individuals who underwent coronary angiography with suspected CAD, and had angiographically normal coronary arteries (NCA) of varying coronary flow rates were enrolled. From the original 77 study participants, forty-seven patients with NCA and SCF in all three coronary vessels and 30 sex- and age-matched control participants with NCA but without SCF were investigated. The quantification of the coronary flow was assessed by use of the TIMI frame count method (TFC) in all coronary arteries. The normal flow was defined as TFC < 28 frames and slow flow as TFC ≥ 28 frames.

Results: HsCRP was significantly positively correlated with mean TFC ($r = 0.522$, $p < 0.001$). In addition, leukocytes, neutrophils and monocytes were significantly positively related to mean TFC ($r = 0.353$, $p = 0.002$; $r = 0.298$, $p = 0.009$ and $r = 0.511$, $p < 0.001$, respectively). In multivariate analyses, only hsCRP (βeta: 0.324, $p = 0.003$) and monocyte count (βeta: 0.354, $p = 0.003$) were related to SCF as determined by TFC.

Conclusion: Our results showed that circulating monocytes and low-grade inflammation are related to SCF. Although we cannot make conclusive assumptions about the underlying pathologic process of SCF, we believe that these findings may be pivotal for further studies which seek to ascertain the specific roles of monocytes and hsCRP on SCF phenomenon in coronary vasculature.

Key Words: Coronary angiography • Coronary artery disease • hsCRP • Leukocytes • Thrombolysis in myocardial infarction • TIMI frame count • Slow coronary flow

INTRODUCTION

Slow coronary flow (SCF) is an angiographic finding characterized by delayed opacification of epicardial coronary arteries in the absence of obstructive coronary disease.[1] It is a relatively common angiographic finding with a reported incidence of 1% in patients undergoing coronary angiography for suspected CAD.[2] Since it was first described in 1972 by Tambe et al., few studies have

Received: August 31, 2011 Accepted: April 25, 2012
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focused on SCF; therefore, the precise pathophysiological mechanisms and clinical importance of SCF are not fully understood. Several mechanisms, however, have been proposed to explain SCF phenomenon, including small vessel disease, microvascular vasomotor dysfunction, diffuse atherosclerosis and endothelial dysfunction.[3-6] Occlusive disease of small coronary arteries, which may be a form of early-phase atherosclerosis, has also been suggested as a cause.[7]

In recent years, it has been recognized that atherogenesis is an active, chronic inflammatory process.[8-10] Inflammation is a central critical feature of atherosclerosis and its clinical manifestations. Numerous epidemiologic and clinical studies have shown leukocytosis and low-grade inflammation to be an independent predictor of future cardiovascular events in patients with CAD, and also in healthy individuals.[11,12] Leukocytes play a major role in these inflammatory processes[10] and may be important in other inflammatory diseases and coronary pathologies as well. Therefore, we aimed to investigate whether there is a positive correlation between leukocyte counts, high-sensitive C-reactive protein (hsCRP) and SCF determined by frame rates.

PATIENTS AND METHODS

The present study was cross-sectional and observational in nature. A total of seventy seven individuals who underwent coronary angiography at our institute's outpatient clinic between May 2009 and December 2010 with suspected CAD and who had angiographically normal coronary arteries (NCA) of varying coronary flow rates without any atherosclerotic lesion were enrolled. The relationship between leukocyte and subtype counts, hsCRP and SCF phenomenon was reviewed.

All patients had chest pain or angina-equivalent symptoms with either positive treadmill test or myocardial perfusion study. Therefore, our patients fulfilled the cardiac syndrome-X criterions including: (1) angina episodes ensuing exclusively or predominantly on effort and typical enough to suggest CAD; (2) findings compatible with myocardial ischemia or coronary blood flow abnormalities during spontaneous or provoked angina; (3) normal coronary arteries at angiography; (4) absence of other specific forms of cardiac disease.

Clinical characteristics, which consisted of multiple descriptors from each patient's history and physical examination, were collected by physicians from the cardiology clinic for each patient at the time of cardiac catheterization and were stored in the database of coronary angiography laboratory at our institution.

Patient selection

Forty-seven patients with NCA and SCF in all three coronary vessels (30 men, 17 women, mean age: 53 ± 10 yrs) and 30 sex- and age-matched control participants with NCA but without SCF (18 men, 12 women, mean age: 51 ± 8 years) were included in the study. Each participant underwent physical and laboratory examinations and was questioned about the risk factors for CAD. Patients with symptomatic peripheral vascular disease (transient ischemic attack, stroke, intermittent claudication, peripheral revascularization, or amputation), an earlier revascularization history with either surgical bypass or percutaneous intervention, evidence of ongoing infection or inflammation, recent acute coronary syndrome, ectatic coronary arteries, valvular heart disease, any form of cardiomyopathies, left ventricular wall motion abnormality assessed by left ventriculography, documented arrhythmia, renal and hepatic dysfunction, hematological disorders and known malignancy or any history of systemic disease were excluded from the study. None of the participants in the study had taken any vasoactive drugs. All of the participants gave informed consent and the study protocol was approved by our institutional investigational review board.

Coronary angiography and determination of slow coronary flow

Coronary angiography was performed by the femoral approach using the standard Judkins technique. Coronary arteries were demonstrated in right and left oblique planes with cranial and caudal angulations and recorded at a film rate of 30 frame/second. Left ventriculography was performed to rule out the presence of left ventricular dysfunction in the right and left anterior oblique views. During the coronary angiography and left ventriculography, iopromide (Ultravist 370, Schering AG, Berlin, Germany) was used as the contrast agent in all patients and control participants.

The patients were assessed for the presence of SCF at coronary angiography, and coronary flow rates were quantified by the thrombolysis in myocardial infarction (TIMI) frame count (TFC) method. For the objective quantification of the coronary flow, two independent observers, who were blinded to the clinical data of the study participants, assessed the coronary flow in coronary arteries using the TFC method, described by Gibson et al.[13] In this method, the number of cine frames, recorded at 30 frames/s, required for the contrast to reach standard distal coronary landmarks in the left anterior descending (LAD), left circumflex (LCX) and right coronary arteries (RCA) were measured. Predefined distal landmarks are the distal bifurcation for the LAD, commonly referred to as the 'pitchfork' or 'whale's tail', the distal bifurcation of the segment with the longest total distance for the LCX, and the first branch of the posterolateral artery for the RCA. In the medical literature, the standard mean values for normal visualization of coronary arteries are described as 36.2 ± 2.6 frames for LAD, 22.2 ± 4.1 frames for LCX, and 20.4 ± 3 frames for RCA.[13] As the LAD coronary artery is usually longer than the other major coronary arteries, the TIMI frame count for this vessel is often higher. Therefore, the TFC for LAD is divided by 1.7 to obtain the corrected TFC (cTFC). The standard cTFC for LAD coronary artery is 21.1 ± 1.5 frames. The mean TFC for each patient and control participant was calculated by dividing the sum of the TIMI frame count of LAD, LCX and RCA by three. In our study, the normal flow was defined as cTFC < 28 frames and slow flow as cTFC ≥ 28 frames. TIMI frame count values were used as a continuous variable, and only in ROC analysis to predict SCF were used as a categorical variable in logistic fashion by the above-described cut-off value.

Total and differential leukocyte counts measurement

Total and differential leukocyte counts and biochemical markers were used for the analysis, which were obtained at most 1 week before coronary angiography. Glucose and lipid profiles were determined by standard methods, and both total and differential leukocyte counts were measured by an automated hematology analyzer (Coulter Gen-S, Coulter Corp., Miami, Florida, USA).

Statistical analysis

Continuous variables were given as mean ± standard deviation; categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov-Smirnov test. The Student's t-test was used for the univariate analysis of the continuous variables, and the $\chi 2$ test for the categorical variables. An optimal cut-off of hsCRP and monocyte count for the detection of SCF was determined by receiver operating characteristics (ROC) analysis based on the results of TFC measurements after comparing sensitivity and specificity at different cut-off values. Linear and logistic regression analyses with the enter method were used for multivariate analysis of independent variables. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (SPSS 15.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

The baseline demographic, clinical and angiographic characteristics of study participants were presented in Table 1.

HsCRP was significantly positively correlated with mean TFC [Overall: $r = 0.522$, $p < 0.001$; in SCF: $r = 0.568$, $p < 0.001$; in NCF: $r = -0.292$, p = non-significant (NS)] (Figure 1A, B). Besides, leukocytes (Overall: $r = 0.353$, $p = 0.002$; in SCF: $r = 0.290$, $p = 0.048$; in NCF: $r = 0.100$, p = NS), neutrophils (Overall: $r = 0.298$, $p = 0.009$; in SCF: $r = 0.371$, $p = 0.010$; in NCF: $r = 0.110$, p = NS) and monocytes (Overall: $r = 0.511$, $p < 0.001$; in SCF: $r = 0.571$, $p < 0.001$; in NCF: $r = -0.157$, p = NS) (Figure 2A, B) were significantly positively related with mean TFC. Similar correlations were also determined separately by TFC values for three coronary arteries (Table 2). When we performed multivariate analysis to determine independent predictors for SCF, only hsCRP (βeta: 0.324, $p = 0.003$) and monocyte count (βeta: 0.354, $p = 0.003$) were related to slow coronary flow determined by TFC. Logistic regression analysis also determined similar results to linear regression analysis (Table 3).

The sensitivity and the specificity of hsCRP and monocyte count to detect SCF in study participants with NCA were evaluated by ROC analysis. The areas under

Table 1. Demographic and clinical characteristics of study participants

Parameters	Overall (N = 77)	SCF (N = 47)	NCF (N = 30)	p value
Age (yrs)	52 ± 9	53 ± 10	51 ± 8	NS
Gender (Male, %)	48 (62%)	30 (64%)	18 (60%)	NS
BMI (kg/m^2)	28 ± 4	28 ± 3.7	27.5 ± 3.6	NS
Waist circumference (cm)	100 ± 9.6	101 ± 10	99 ± 9	NS
Systolic BP (mmHg)	128 ± 17	128 ± 18	129 ± 15	NS
Diastolic BP (mmHg)	79 ± 10	80 ± 10	78 ± 9	NS
Hypertension, n (%)	41 (53%)	25 (53%)	16 (53%)	NS
Diabetes mellitus, n (%)	11 (14%)	7 (15%)	4 (13%)	NS
Hyperlipidemia, n (%)	32 (42%)	19 (40%)	13 (43%)	NS
Cigarette smoking, n (%)	32 (42%)	18 (38%)	14 (47%)	NS
Fasting glucose (mg/dl)	94 ± 49	99 ± 62	86 ± 11	NS
Total cholesterol (mg/dl)	187 ± 34	188 ± 39	186 ± 26	NS
Triglycerides (mg/dl)	159 ± 72	163 ± 80	154 ± 58	NS
HDL cholesterol (mg/dl)	37 ± 8	37 ± 9	37 ± 5	NS
LDL cholesterol (mg/dl)	119 ± 27	118 ± 31	120 ± 21	NS
Hemoglobin (mg/dl)	14.7 ± 1.4	14.8 ± 1.6	14.6 ± 1.1	NS
Hematocrit (%)	43.4 ± 4.7	43.6 ± 4.7	43.1 ± 4.8	NS
Platelet (10^3/mm^3)	241 ± 52	241 ± 52	241 ± 51	NS
Total leukocyte (/mm^3)	7170 ± 1149	7460 ± 1229	6717 ± 850	0.005
Neutrophil (/mm^3)	4376 ± 819	4538 ± 888	4122 ± 630	0.028
Monocyte (/mm^3)	567 ± 137	617 ± 130	488 ± 110	< 0.001
HsCRP (mg/dl)	0.7 ± 0.5	0.9 ± 0.5	0.4 ± 0.3	< 0.001
TIMI frame count measurements				
LAD (corrected)	34.6 ± 9.6	42.1 ± 2.2	22.9 ± 1.9	< 0.001
LCx	32.8 ± 10.1	40.6 ± 2.3	20.5 ± 2.1	< 0.001
RCA	31.1 ± 8.7	37.9 ± 1.2	20.6 ± 2.3	< 0.001
Mean	32.9 ± 9.4	40.2 ± 1.8	21.3 ± 1.3	< 0.001

BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; HsCRP, high sensitive CRP; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LDL, low density lipoprotein; NCF, normal coronary flow; NS, not significant; RCA, right coronary artery; SCF, slow coronary flow; TIMI, thrombolysis in myocardial infarction.

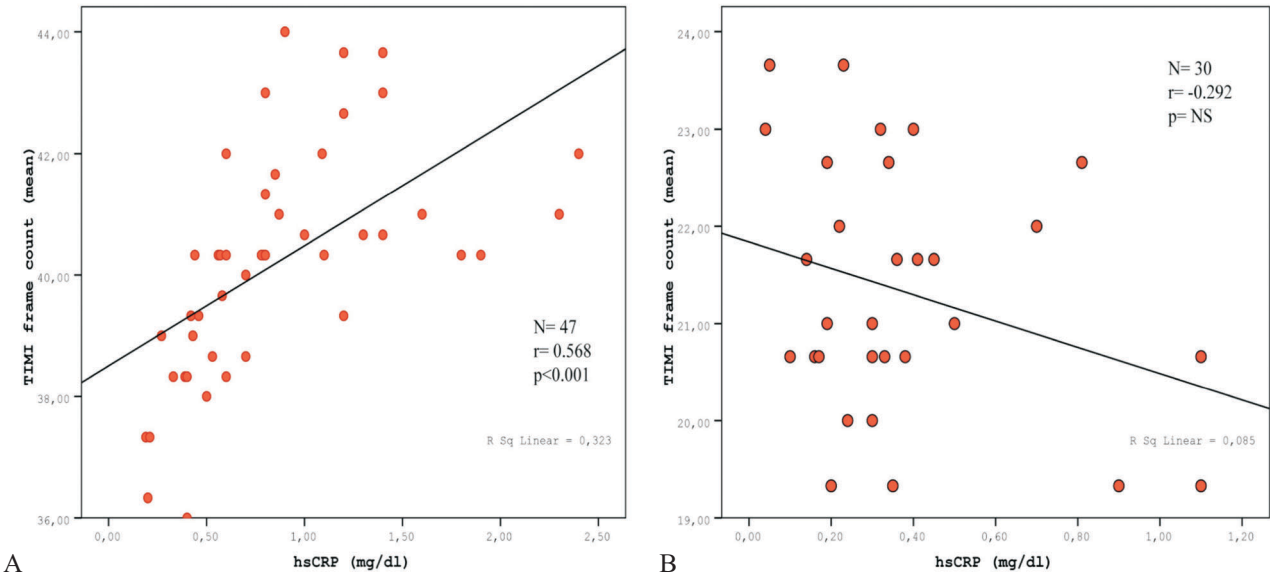

Figure 1. *The correlation of hsCRP with mean TIMI frame count in patients with SCF (A) and NCF (B). SCF, slow coronary flow; NCF, normal coronary flow.*

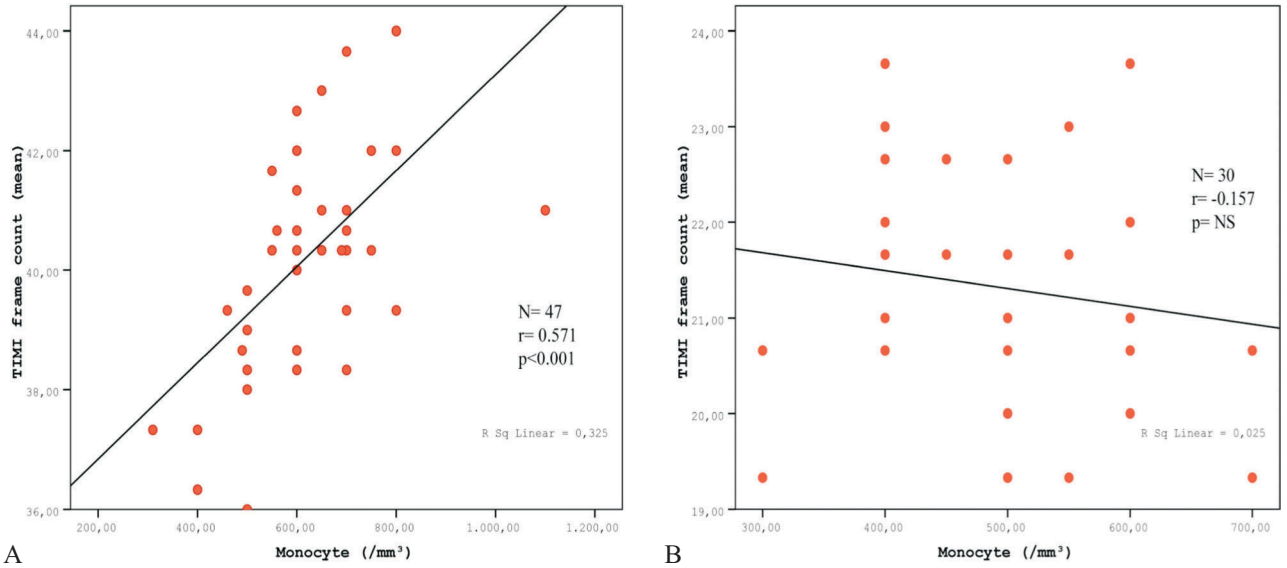

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Figure 2. *The correlation of monocyte counts with mean TIMI frame count in patients with SCF (A) and NCF (B). SCF, slow coronary flow; NCF, normal coronary flow.*

Table 2. Correlations of the coronary flow rate with circulating inflammatory cells and hsCRP

N = 77	TIMI frame counts (TFC) for three coronary arteries			
Variables	Mean TFC	LAD (corrected)	LCx	RCA
HsCRP (mg/dl)	r = 0.522, p < 0.001	r = 0.533, p < 0.001	r = 0.532, p < 0.001	r = 0.486, p < 0.001
Leukocytes (/mm^3)	r = 0.353, p = 0.002	r = 0.349, p = 0.002	r = 0.369, p = 0.001	r = 0.330, p = 0.003
Neutrophil (/mm^3)	r = 0.298, p = 0.009	r = 0.298, p = 0.008	r = 0.312, p = 0.006	r = 0.274, p = 0.016
Monocyte (/mm^3)	r = 0.511, p < 0.001	r = 0.522, p < 0.001	r = 0.517, p < 0.001	r = 0.481, p < 0.001

HsCRP, high sensitive c-reactive protein; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

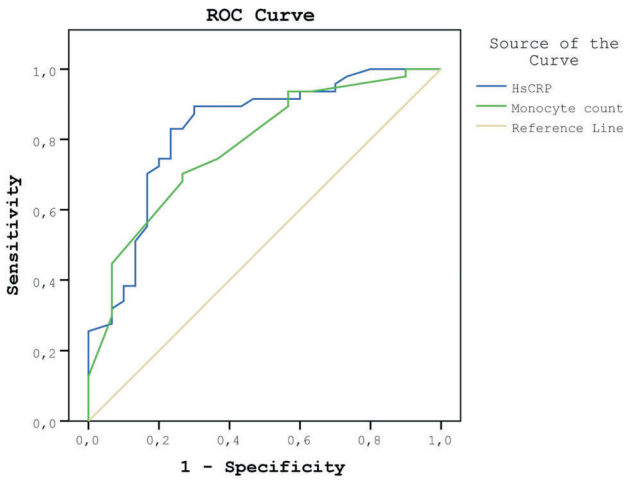
Table 3. The independent effects of hsCRP and monocytes on slow coronary flow phenomenon

N = 77	Mean TFC (Dependent variable)			SCF (Dependent variable)	
Variables	β ± SE	Beta	p value*	OR (95%CI)	p value*
Age (yrs)	0.1 ± 0.1	0.06	0.586	1.021 (0.948-1.100)	0.583
Gender (male)	0.4 ± 1.9	0.02	0.852	0.996 (0.285-3.478)	0.995
Hypertension	0.2 ± 1.9	0.01	0.910	1.470 (0.438-4.931)	0.532
Diabetes Mellitus	2.3 ± 2.5	0.1	0.413	2.074 (0.332-12.95)	0.435
Smoking	-0.2.1 ± 2.0	-0.1	0.306	0.313 (0.075-1.311)	0.112
Hyperlipidemia	-2.9 ± 2.1	-0.2	0.168	0.353 (0.079-1.582)	0.174
HsCRP (mg/dl)†	6.5 ± 2.1	0.347	0.003	1.390 (1.106-1.746)	0.005
Monocyte (/mm^3)	0.02 ± 0.01	0.354	0.003	1.008 (1.002-1.014)	0.010
Neutrophil (/mm^3)	0.001 ± 0.001	0.1	0.534	1.001 (0.999-1.001)	0.744
Constant	13 ± 7	-	0.062	0.002	0.024
R^2	0.376			0.488	

* Linear and logistic regression analyses with enter method were used for multivariate analysis of independent variables; † for per 0.1-mg/dL increase in hsCRP level.

ROC were found as 0.827 ($p < 0.001$, 95% CI: 0.729-0.925) and 0.781 ($p < 0.001$, 95% CI: 0.677-0.885), respectively (Figure 3).

The hsCRP and monocyte count were found to be specific and sensitive for the detection of SCF. When 0.52 mg/dl was accepted as the cut-off value for hsCRP, the sensitivity and the specificity for the detection of SCF were 70% and 83%, respectively. When 555 cell/mm^3 was accepted as the cut-off value for monocyte count, the sensitivity and the specificity for the detection of SCF were 70% and 73%, respectively.



	AUC	SE	p value	95% CI
HsCRP	0.827	0.050	< 0.001	0.729-0.925
Monocyte	0.781	0.053	< 0.001	0.677-0.885

Figure 3. *The sensitivity and the specificity of hsCRP and monocyte count to detect the slow coronary flow in patients with angiographically normal coronary artery. HsCRP, high sensitive CRP; AUC, area under the curve; SE, standard error.*

DISCUSSION

This study aimed to investigate whether circulating inflammatory cells and inflammatory status are related to SCF. The major finding of our study was a positive correlation between leukocyte counts, hsCRP and slow coronary flow determined by frame rates.

Although the exact pathophysiological mechanism of SCF has not been consistently established, there are several mechanisms suggested to be involved in the development of SCF. The first hypothesis that small vessel dysfunction contributes to the pathogenesis of SCF was proposed by Tambe et al.[1] and was confirmed by a histopathological study by Mangieri et al., which demonstrated microvascular abnormalities in patients with SCF.[3] In addition, Kurtoglu et al.[14] reported an improvement in microvascular tone and coronary flow with microvascular vasodilators suggesting a functional increase in microvascular resistance. In contrast, intravascular ultrasound studies identified epicardial coronary artery disease as a pathophysiological factor for SCF, as well as microvessel disease.[4,15,16] Accordingly, it has been concluded that abnormal slow flow pattern in coronary arteries may be a manifestation of diffuse atherosclerotic disease by damaging endothelium without creating an angiographically visible coronary lesion,[16] and SCF could be an early manifestation of diffuse atherosclerosis involving both the microvascular system and epicardial coronary arteries.[4] These observations suggest that a pathophysiologically relevant interaction exists between SCF phenomenon and endothelial dysfunction.

Blood-borne inflammatory and immune cells constitute an important part of an atherosclerotic plaque. Recent studies have shown that inflammatory cells, especially monocytes, dominate in early atherosclerotic lesions. Their functional molecules accelerate progression of the lesions, and activation of inflammation to elicit an acute coronary syndrome. The pathogenesis of atherosclerosis is multifactorial; however, the role of inflammatory cells such as monocytes and lymphocytes for plaque formation is clear.[17,21-25]

In a study by Chapman et al., the monocyte count in blood was found to be a better cross-sectional marker of plaque presence than interleukin-6 (IL-6), hsCRP, fibrinogen, and white blood cells.[21] Furthermore, Johnsen et al. showed that monocyte count was an independent predictor of future plaque formation.[22] Excluding patients with chronic kidney disease, cross-sectional studies reported increased numbers of circulating monocytes in individuals with prevalent atherosclerotic disease.[23,24] Additionally, prospective studies suggested that monocyte count can predict cardiovascular events independently.[25,26]

The precise pathophysiological mechanism of the SCF phenomenon still remains uncertain. Small vessel abnormality and dysfunction have been implicated in its pathogenesis.[1] Mangieri et al. reported histopathological

findings in left ventricular endomyocardial biopsy specimens in a group of 10 patients with SCF without any other cardiac or systemic diseases.[3] They showed evidence for small vessel abnormality as endothelial thickening due to cell edema, capillary damage, and reduced luminal diameter of the small vessels. Additionally, inflammation,[27,28] platelet function disorder[29,30] and imbalance of vasoactive substances[31,32] have also been implicated in the pathogenesis of the SCF phenomenon. Serum paraoxonase (PON) is a high-density lipoprotein bound antioxidant enzyme that inhibits atherosclerosis and endothelial dysfunction. Yıldız et al.[33] reported that serum PON activity was independently associated with the mean TFC, suggesting that reduced serum PON activity might represent a biochemical marker of SCF. Enli et al.[34] showed that patients with SCF had significantly increased serum malondialdehyde and erythrocyte superoxide dismutase levels and decreased erythrocyte-reduced glutathione levels compared to patients with normal coronary flow. These findings indicate that free radical damage may play a role in the pathogenesis of SCF.

Coronary microvasculature, with small-diameter and well-developed media, is the major vascular determinant of coronary vascular resistance.[35] Atherosclerosis and dysfunction of coronary microvasculature are well-known pathophysiologic mechanisms of SCF.[7] In a recent article, Erdoğan et al.[36] reported that the coronary flow reserve, which reflects coronary microvascular function, was impaired in patients with SCF and corrected TFC was correlated with coronary flow reserve. In a prior study,[37] hsCRP was found to be significantly higher in patients with SCF compared to normal control group. However, leukocyte count was not different between the SCF and the normal group. In our study, the effect of hsCRP on SCF was confirmed. On the other hand, leukocyte count was also related to SCF, but multivariate analysis showed that specifically monocyte count, and hsCRP are independently related with SCF. Therefore, our results add new information on this research area with monocytes as well as hsCRP.

If hsCRP and monocytes have pathogenetic effects on endothelial cells and/or subendothelial structure of the vessel wall by means of the previously discussed mechanisms, these mechanisms may be further investigated for treatment of patients with SCF.

STUDY LIMITATIONS

Our study had some limitations. First of all, the study population was relatively small and a larger study population would provide enhanced statistical reliability. The main limitation of our study is that it does not explain the exact mechanism of the relationship between elevated leukocyte counts and SCF. In the current study, to decrease confounding factors for SCF, we used more extensive specific inclusion and exclusion criterions. In addition, TFC measurements were used to determine coronary flow rates. On the other hand, coronary velocities may be measured as cm/sec in coronary arteries, or specifically the measurement of diastolic coronary flow by Doppler echocardiography (peak diastolic velocity in cm/sec) might be more physiological than TFC measurement in which coronary flow velocity is measured as a mean rate which involved systolic and diastolic intervals. Slow coronary flow is related to dilated coronary vessels; therefore, patients with ectatic coronary arteries in our study were excluded because of its confounding effect on coronary flow. On the other hand, the diameter of proximal coronary vessels was not used for any adjustment or analysis, which this may be a study limitation.

Lastly, in our study, the control group included patients who are not completely normal. Although they have angiographically normal coronary arteries, they still have cardiac risk factors or may have cardiac syndrome-X. Therefore, the statistical differences would be difficult to determine between the normal and the pathologic group. Nonetheless, our study population revealed many significant relations between the study groups.

CONCLUSION

Our results showed that circulating monocytes and low-grade inflammation are related to SCF. Although we cannot conclude the underlying pathologic process of SCF, we believe that these findings may be pivotal for further studies which seek to establish the specific roles of monocytes and hsCRP in the SCF phenomenon in coronary vasculature.

DISCLOSURES

We disclose that there is no relationship with industry or any conflict of interest in our study.

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