Comparison of Plasma Level of hs-CRP in Subjects with Slow Coronary Flow and Normal Coronary Flow

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Abstract

Introduction-Slow Coronary Flow (SCF) is defined as a condition in which in spite of no evidence of coronary occlusion or stenosis in angiography, there is delayed opacification of the vessels after the injection of a radiocontrast agent. First endothelial dysfunction and later on inflammation and platelet dysfunction have been proposed in the pathogenesis of this phenomenon. Because of a lack of enough studies about this disorder and controversy in reports, in the present study the prevalence rate of SCF and the probable role of inflammatory factors were investigated in order to identify the etiology of SCF and improve the treatment process of patients.

Method-This descriptive-analytic study was performed by studying the angiograms of 1162 patients with a probable diagnosis of coronary vessels stenosis who underwent coronary angiography in Shafa Hospital (Kerman/Iran). Angiography was performed by standard method of Judkins technique and statistical analysis was done to find the cut-off point value for the selection of the SCF group. After the angiograms had been examined by two cardiologists, 40 individuals with SCF and 40 ones with normal coronary flow (NCF) were investigated.

Results- The prevalence rate of SCF in the subjects that underwent angiography was 4.13% and 60% of them were male. Plasma level of hs-CRP in both study groups was slightly higher than the normal and there was no significant difference between the two groups.

Conclusion- The role of inflammatory factors as an underlying factor in the incidence of SCF was not confirmed***(Iranian Heart Journal 2012; 13 (1):17 -22*).**

Keywords: Timi frame count■ Slow coronary flow■ Coronary angiography■ High sensitive CRP

According to the previous studies, approximately 10-20% of patients undergoing coronary angiography due to typical pains of angina pectoris have no occlusion or stenosis in coronary vessels so that they are labeled X syndrome.[1] This syndrome includes a heterogeneous group containing slow coronary flow (SCF) too. The prevalence rate of SCF has been estimated as 1-3%, even though Mahgieri et al. reported a higher prevalence rate of 7%.[3]

This phenomenon was introduced for the first time in 1972 by Tambe et al. and defined as delayed opacification of vessels in angiography in spite of the absence of any occlusion or stenosis in coronary arteries (1). A number of theories such as endothelial dysfunction, vasomotor neurons dysfunction, microvascular flow dysfunction, and platelet dysfunction have been proposed as the causing factors.[9] Later on, the relationship of SCF with the elevation of some inflammatory

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markers in the blood such as endothelin-1 and C-reactive protein (CRP) was suggested[9], although this relationship was rejected by some other studies.[20] In a study performed in Medical Sciences Academy of China, several theories, including increase of blood viscosity and plasma level of fibrinogen, imbalance between vasodilator and vasoconstrictor factors, platelet dysfunction and finally inflammatory factors, were mentioned in the pathology of CSF.[9] In a study performed in Afyon University in Turkey, the researchers claimed that they were the first ones to have proved the role of inflammation in SCF.[2] Hassani Ari et al., in their study in 2010, emphasized the role of endothelial dysfunction in the etiopathology of SCF and rejected the role of inflammatory factors.[20] Because of these controversies about the role of inflammation in SCF and a lack of related studies in Iran, as well as the lower mean age of Iranian patients compared to those in Western countries, the present study was designed to find the prevalence rate of SCF in an Iranian population and its relationship with inflammatory factors such as hs-CRP.

Patients and Methods

This descriptive-analytic study (from July 2010 to May 2011) was performed on 1162 patients who underwent coronary arteries angiography in Shafa Hospital, Kerman/Iran due to complaining of recurrent chest pains and in some cases with a history of hospitalization in the CCU. Angiography was performed via the Judkins technique through femoral artery and use of 6f catheter for the manual injection of 6-8ml Visipaque for each view. No special medication affecting vessels resistance was used. Angiograms were reviewed daily by two cardiologists, and patients with no stenosis, occlusion, or coronary vessels ectasia (regardless of normal or slow blood flow) were specified. Meanwhile, coronary arteries vessel diameter was measured by quantitative computer-assisted (QCA) method; and in the case of being less than 3 mm, the patient was excluded from the study.

Exclusion criteria

1. Coronary artery disease 2. Heart failure according to echocardiography (EF<55%), 3. Left ventricular hypertrophy, 4. Congenital or valvular heart diseases, 5. Renal dysfunction (creatinine >1.5), 6. Previous history of myocardial infarction or coronary angioplasty or surgery, 7. History of malignancy, 8. Disorders of gastrointestinal tract motility, 9. Uncontrolled hypertension, 10. History of surgical operation in the last three weeks, 11. Metabolic diseases or uncontrolled diabetes and insulin-dependent diabetes, 12. Consumption of corticosteroids, estrogen or cytotoxic drugs, 13. History of significant infection in the last 6 months, 14. Hyperlipidemia under treatment (LDL≥160, TG≥200), 15. Thyroid and autoimmune diseases, and 16. History of connective tissue diseases.

It should be mentioned that the above conditions either increase hs-CRP or affect coronary blood flow velocity (17). Eight of the 48 SCF patients and 9 of the 49 NCF individuals were excluded based on the above exclusion criteria.

Data analysis

Mean ±SD was used for the presentation of the descriptive data. For the qualitative data, frequency distribution and relative frequency were used. The chi-square test was used for comparison of the qualitative data and the Student *t*-test for the comparison of the quantitative data between the two groups. The Pearson correlation test was applied to determine the relationship between the mean TIMI frame count and serum hs-CRP level in each group. Receiver Operative C-Curve was used to find a cut-off value for hs-CRP, mean TIMI frame count, RCA, LCX and corrected LAD. For this, points with their sensitivity and specificity for each of the mentioned factors were determined. Data analysis was done through SPSS software package and

$p<0.05$ was considered a statistically significant level.

Slow coronary flow diagnosis criteria

TIMI frame count, the number of frames from the onset of vessel visualization until its complete visualization in coronary vessels angiography, is an exact criterion for blood flow velocity. In other words, a higher frame count shows a longer time for complete visualization of the vessel and this time is a function of blood flow velocity and length of vessel. Since according to Gibson et al. study, left anterior descending (LAD) is 1.7 times longer than circumflex (LCX) and right coronary (RCA) arteries, the longer frame count of this artery can be corrected through dividing it by 1.7. In statistical analysis, cut-off point value for determining the SCF group, by considering the number of frame count in normal arteries, was found to be 22.5 for the RCA (sensitivity= 97.5% and specificity= 100%), 26 for the LAD (sensitivity= 97.5% and specificity= 100%), and 28 for the LCX (sensitivity and specificity=100%). Considering the mentioned criteria, 48 subjects were diagnosed as SCF cases and 240 ones as NCF subjects. Among the NCF subjects, 49 persons were randomly selected as the control group**.** The aims of study were explained to all the subjects; and after obtaining their informed consent, physical examination, vital signs control, laboratory tests, echocardiography, filling out the questionnaires and considering exclusion criteria, 40 patients from each group were selected to determine their hs-CRP level. hs-CRP is a very good marker of inflammation in cardiovascular diseases and hs-CRP>3mg/L is associated with increased incidence of cardiovascular events.[18] Following infections, the blood level of this marker remains high for several weeks and in connective tissue diseases, chronic renal failure, acute myocardial infarction, and obese patients, this marker level increases. CRP level does not change in different hours of day and its measurement does not require fasting.[17] Blood level of hs-CRP was determined by turbidometry (high sensitivity latex) method Cat No 046289/8by automatic cobas integra400 (Roche company, Germany) instruments and was reported based on mg/L.

Results

From a total of 1162 subjects, 48 patients (4.13%) were included in the SCF group and 240 (20.65%) in the NCF group; the others were excluded due to coronary artery stenosis. In the SCF group, 52% and in the NCF group, 42.5% had a history of CCU hospitalization. As it is seen in Table 1, there was no significant difference between the two groups based on age, BMI, history of diabetes, hypertension, cigarette smoking, addiction and consumption of drugs, but in regard to sex, the number of male patients in the SCF group was higher ($p<0.001$). Therefore, multi-purpose linear Regression was used to omit the effect of sex and the results again showed no significant difference between the two groups in hs-CRP level.

As regards mean TIMI frame count in three coronary arteries and with correction for the LAD, a significant difference ($p<0.001$) was found between the SCF group (37.5±5.4) and the NCF group (18.9±2.1) (Table II).

In both groups, hs-CRP was higher than the maximum normal level, but the difference between the two groups was not statistically significant.

Figure 1 shows the Scatter plot graph of the correlation between mean TIMI frame count and hs-CRP level in the two groups. The Pearson correlation test showed no significant correlation between these two variables in the NCF group ($r=0.05$, $P=0.75$) and in the SCF group.

TableI. Demographic features and consumed drugs in the two study groups

Group / Variable	NCF N (%)	SCF N (%)	P value
Age (Mean± SD)	50.6±9.9	48.6±7.9	0.32 **NS**
Sex (male)	8 (20%)	24 (60%)	0.001
BMI (Mean± SD)	24.9±3.4	25.5±3.6	0.49 **NS**
Diabetes mellitus	4 (10)	3 (7.5)	NS
Hypertension	14 (53)	11 (27.5)	NS
Cigarette smoking	6 (15)	8 (20)	NS
Opium-dependency	8 (20)	7 (17.5)	NS
CCU admission	17 (42.5)	21 (52.5)	NS
Consumed drugs:			
beta-blockers	27 (67.5)	29 (72.5)	NS
Statins	31 (77.5)	29 (72.5)	NS
Nitrates	29 (72.5)	31 (77.5)	NS
ACEI	2 (5)	6 (15)	NS
ARB	1 (2.5)	0 (0)	NS
Calcium blocker	7 (17.5)	5 (12.5)	NS
Aspirin	35 (87.5)	33 (82.5)	NS
NSAIDs	0 (0)	0 (0)	NS

NS: non-significant, ACEI= Ang II converting enzyme inhibitor, ARB= Ang II receptor blocker, BMI = body mass index

Table II. Comparison of the two study groups in regard to serum level of hs-CRP and TIMI frame count

Group / Variable	NCF (n=40)	SCF (n=40)	P value
hs-CRP	3.32±3.3	4.3±5.2	0.31
LCX	19.9±2.5	38.1±5.3	<0.001
RCA	17.5±2.2	34.05±7.8	<0.001
Corrected LAD	19.32±2.2	35.01±7.4	<0.001
TIMI frame count	18.9±2.01	35.7±5.7	<0.001

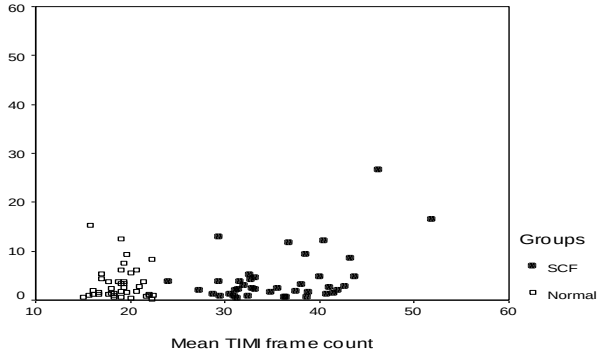

Fig.1. correlation of hs-CRP and mean TIMI frame count in the two groups

Discussion

Despite the fact that frequent risk factors for atherosclerotic coronary artery disease have been extensively studied, there are limited data about the etiology and clinical manifestation of CSF phenomenon, and specific data on underlying predisposing factors for this phenomenon are insufficient in the medical literature.[21]

Recent reports have estimated an incidence of 7% of this phenomenon in patients suspected to have cardiovascular disease.[7] In those reports, the main clinical features of CSFP were young age, chest discomfort, or angina pectoris for a longer duration without accompanying cardiovascular disease or any coronary risk factors or muscle bridge by angiographic examination; nevertheless, they show significant CSFP in multiple vessles.[21]

Although inflammation is recognized as an initiating and progressive factor in atherosclerosis and the serum level of inflammatory markers is even used as a predictive factor in cardiovascular events, in the present study, the role of inflammatory factors in the incidence of SCF was not confirmed. The results of this study are in agreement with the results of the Hassan Ari et al. study, in which no significant difference in CRP level was found between SCF and NCF groups.[20] However, there are other studies with different results. For example, Jian Junli et al. performed a study on 42 patients with SCF who were mostly male subjects (75%), similar to our study with 60% male subjects, and after measuring CRP and IL.6, they introduced chronic inflammation as a probable factor in SCF incidence.[9] Ahmet Camsari et al. reported endothelial dysfunction in SCF patients.[19] Although SCF phenomenon was introduced in 1972[1], there is practically no sufficient studies about it. Since inflammatory phenomenon can be seen in several other diseases and conditions, there are relatively many exclusion criteria. In the present study, more exclusion criteria were considered compared to similar studies and

led to the exclusion of 7 cases from the SCF group and 8 from the NCF group. Moreover, because some studies have mentioned that some factors such as nitrate consumption, the number of heart beats, and catheter size can affect the number of frame count in angiography[20], in the present study, all the patients underwent angiography with the Judkins catheter size 6f and there was no significant difference between the two groups in regard to nitrate consumption (see Table I). The number of heart beats at the time of angiography was not recorded but it did not seem to be different between the two groups. Meanwhile, both groups were matched regarding consumption of medications affecting CRP level (see Table I).

Study limitations

A large number of subjects in the control group, in spite of having normal coronary arteries, were complaining of typical angina pectoris and for this reason they were under treatment with medication. It should be noted that normal coronary angiogram cannot completely reject atherosclerosis in these patients. Due to the invasiveness of angiography, its application to individuals without any cardiac problem is practically contraindicated. In case of intravascular ultrasound examination, it can be recognized that in spite of normal coronary angiogram the vessel wall has atherosclerotic plaques in some cases. Unfortunately, we did not have this facility in our center.

Overall, although in the present study the role of inflammatory process in the pathology of SCF was not confirmed, the probability of platelet dysfunction and slow blood flow in the vessels of these patients, the administration of statins and anti-platelet medications seems to be a logical recommendation. The follow-up of the subjects who participated in the present study can help diagnose the disease progress and answer many related questions.

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