

Vascular Inflammation and Angiographic Severity of Coronary Artery Disease in Young Asian Indians

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ABSTRACT

Background: By 2015, India will have the largest coronary artery disease (CAD) burden in the world. Indians manifest CAD at a younger age. Inflammation plays a key role in CAD progression. Inflammatory marker high sensitivity C-reactive protein (hsCRP) predicts CAD risk either by correlation with CAD extent (disease marker) or as an indicator of inflammatory event that leads to plaque rupture (a process marker). **Aim:** To assess the role of vascular inflammation and correlate with coronary atherosclerosis in an economically and relevant section of population of young Indians. **Methods:** Serum hs-CRP (measured by immune-turbidimetry technique) level was measured in young adults (18–45 years) with angiographic proven CAD (60 patients), and compared with those >45 years age (24 patients), and in controls with no CAD (14 patients). Later, the levels of hs-CRP were compared with the angiographic stenosis and extent score in young CAD patients. **Results:** Mean hsCRP was elevated in Young CAD patients more than in those of Old CAD patients and Controls, and this trend was found to be significant by ANOVA ($P = 0.028$). The hs-CRP levels were found to be in direct proportion to both stenosis and extent score of coronary artery disease ($P < 0.01$) in young adults. **Conclusion:** Serum hs-CRP levels and inflammation have a positive correlation with the disease burden in the young CAD patient. Premature CAD in Young Asian Indians could be partly explained by increased vascular inflammation. Further studies and interventions to identify & reduce risk factors in an economically and socially relevant section of population of a fast developing country like India is urgently needed.

Keywords: Angiographic stenosis, Angiographic extent, hs-CRP, Young coronary artery disease.

INTRODUCTION

By the year 2015, India will have the largest coronary artery disease burden in the world¹. Indian populations are more prone to develop CAD at a younger age. Symptoms of CAD arise a full 10 years earlier in India than in Western countries². Half of the cardiovascular disease (CVD) -related deaths (ie, 52% of CVDs) in India occur below the age of 50 years, and about 25% of acute

myocardial infarction (MI) in India occurs under the age of 40 years³. Fewer studies on epidemiological data from angiographically proven cases of premature CAD (≤ 40 –45 years) in native Indians are available⁴.

Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis. C-reactive Protein (CRP), an inflammatory biomarker, has independently emerged as one of the most powerful predictors of cardiovascular disease⁵. However, the relationship between levels of hs-CRP and the presence and extent of angiographically documented coronary artery disease have seldom been investigated in the Indian context, especially in young adults. It is possible that CRP is predictive for CAD risk either through a correlation

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with CAD extent (disease marker) or as an indicator of inflammation that leads to an atherothrombotic event that leads to plaque rupture (a process marker)⁶. Defining the relationship between CRP and disease markers such as CAD extent as assessed by coronary angiography in young Indians, would help in assessing role of inflammation in the occurrence of CAD in an economically and socially relevant section of population of a fast developing country like India.

MATERIAL AND METHODS

Patient population: This study included 100 patients admitted with IHD and undergone coronary angiography (CAG) in the Department of Cardiology, ICVS, IPGMER/ S.S.K.M. Hospital, Kolkata. Sixty patients ≤ 45 yrs of age, both males and females, admitted with IHD were enrolled in this study as the test population of “young adults with CAD”. Forty patients (> 45 yrs of age or those with normal coronaries), both males and females, admitted with IHD were enrolled in this study as “controls”. The patients with history of coronary angiography in the recent past, on statins for more than one month, any systemic infection, collagen vascular disease, recent trauma, pregnancy and patients with documented extra-cardiac atherosclerosis were excluded from the study.

Study design: It was a cross-sectional case control study. Among the selected cases, the test group of patients with age < 45 years age were labelled as “Young CAD” group and those with age > 45 years age were labelled as “Old CAD” group. The patients who had chest pain but normal coronary angiograms were taken as control subjects (labelled as “controls”).

Angiographic estimation of coronary atherosclerosis: Coronary angiography was performed by the femoral approach and included at least 4 views of the left coronary artery and 2 views of the right coronary artery.

Stenosis Score: Stenosis Score used was a modified Genini score⁷. Stenosis score provides information related to the bulk of the atherosclerotic lesion and is influenced by episodic processes such as plaque rupture. Each of eight vessel segments was graded according to severity of occlusion; grade 1 for 1% to 49% occlusion in lumen diameter, 2 for 50% to 74%, 3 for 75% to 99%, and 4 for total occlusion. The score in each of the eight segments were added to give a total score out of theoretical maximum of 32. This score therefore, places emphasis on the

severity of stenosis, while including some of the extent of CAD.

Extent score: Extent score used was a David R. Sullivan's new angiographic score of the extent of coronary artery disease⁸. The score indicates the proportion of the coronary arterial tree involved by angiographically detectable atheroma. The proportion of each vessel involved by atheroma, identified by luminal irregularity, was multiplied by the factor for each vessel. Left main artery, 5; left anterior descending, 20; main diagonal branch, 10; first septal perforator, 5; left circumflex artery, 20; obtuse marginal and posterolateral vessels, 10; right coronary artery, 20; and main posterior descending branch, 10. When a vessel was occluded and the distal vessel not fully visualised by collateral flow, the proportion of vessel not visualised was given the mean extent score of the remaining vessels. When the major lateral wall branch was a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the left circumflex artery a factor of 10. The score for each vessel or branch were added to give a total score out of 100, that is the percentage of coronary intimal surface area involved by atheroma.

hs-CRP estimation: The CRP test was performed by using UBI MAGIWEL CRP-quantitative AD-401 kit, a solid phase enzyme linked immunosorbent assay (ELISA) as per instructions of the manufacturer (supplied with kit).

Statistical Analysis: Data were analysed with SPSS for windows statistical package and are presented as mean \pm SD. Univariate comparison between groups were made with nonparametric test; Kruskal-Wallis test for multi-group comparison and Mann-Whitneys test for 2-group comparison. Discrete variables were compared with chi square test. The correlation between levels of hs-CRP and angiographic stenosis and extent was assessed by Pearson's correlation. For all results, a P value of < 0.05 was considered significant⁹.

RESULTS

Out of 60 Young CAD (41 males) patients, 42 presented as acute coronary syndrome and the rest 18 as chronic stable angina. Out of 24 Old CAD (15 males) patients, 14 presented as acute coronary syndrome and the rest 10 as chronic stable angina. There were 16 patients (12 males) in the control group of normal coronaries.

The three groups were comparable with respect to age, sex, and other risk factors for coronary artery disease such as diabetes, hypertension, dyslipidemia, obesity and smoking. (Table 1)

Table 1 Baseline clinical characteristics of the study population.

	YOUNG CAD N (%)	OLD CAD N (%)	CONTROLS N (%)
SMOKER	22 (36.7%)	9 (37.5%)	5 (31.3%)
HTN	20 (33.3%)	8 (33.3%)	5 (31.3%)
DM	14 (23.3%)	8 (33.3%)	4 (25%)
OBESITY	20 (33.3%)	6 (25%)	4 (25%)
DYSLIPIDEMIA	46 (76.7%)	20 (83.3%)	14 (87.5%)
MEAN AGE (Yrs)	39.1	65.5	52.1

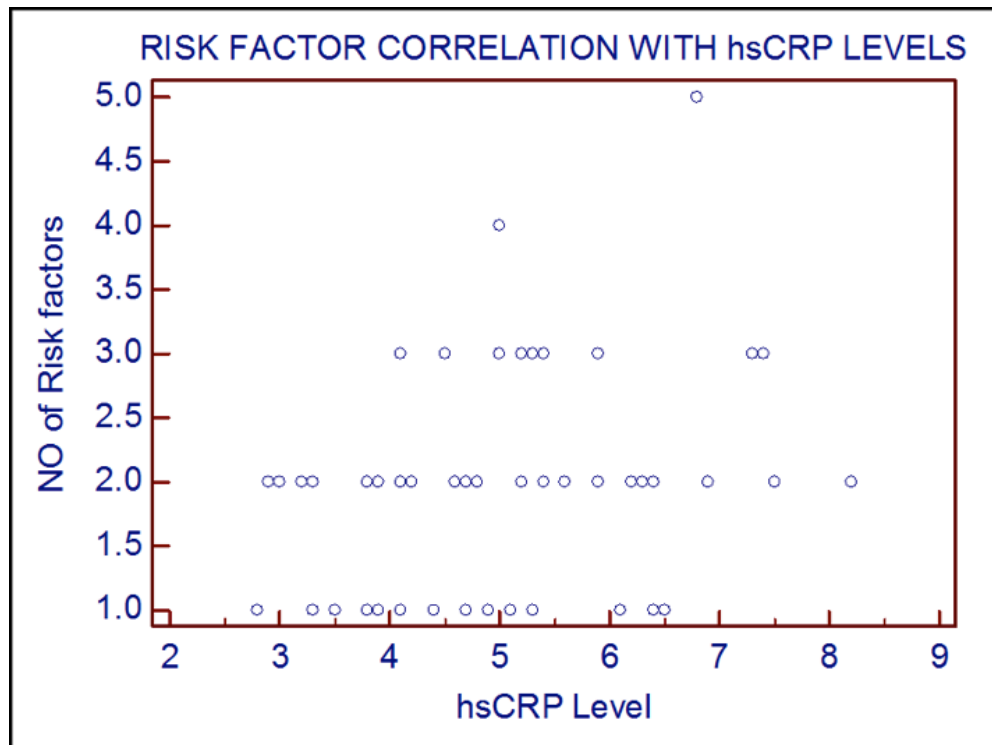
P> 0.05 in all the above variables, they are comparable.

Out of 60 Young CAD patients, 18 had 1 cardiovascular (CV) risk factor, 29 had 2 CV risk factors, 11 had 3 CV risk factors, 1 each had 4 or 5 CV risk factors. Pearson's correlation revealed significant positive correlations

of serum hsCRP levels with number of risk factors in the Young CAD group ($P=0.011$, $r=0.3253$, 95% CI = 0.07775 to 0.5350).(Table 2, Figure 1)

Table 2 Distribution of Risk Factors Among CAD Age Groups

	YOUNG CAD N (%)	OLD CAD N (%)	CONTROLS N (%)
0 RISK FACTOR	0	0	1 (6.25%)
1 RISK FACTOR	18 (30%)	7 (29.2%)	4 (25%)
2 RISK FACTORS	29 (48.3%)	10 (41.7%)	6 (37.5%)
3 RISK FACTORS	11 (18.3%)	5 (20.8%)	4 (25%)
4 RISK FACTORS	1 (1.7%)	2 (8.3%)	1 (6.25%)
5 RISK FACTORS	1 (1.7%)	0	0

**Figure 1:** Risk Factor Correlation with hsCRP Levels in Young CAD

Patients with ACS had the highest mean hs-CRP levels among both young CAD (5.60 mg/l) and old CAD (3.53 mg/l) patient groups. Mean hsCRP in chronic stable angina patients was 3.89 mg/l in young CAD group and 2.95 mg/l in the old CAD group. Mean hsCRP was significantly elevated in both ACS Group ($P = <0.01$) and CSA Group ($P = 0.02$) of Young CAD patients than in those of Old CAD patients. When compared among

age groups in total, mean hsCRP showed a trend which was maximum in the young CAD group (5.0 mg/l), followed by the old CAD patient group (3.40 mg/l) and least in the control group of individuals with normal coronaries (2.30 mg/l). Mean hsCRP was therefore, elevated in Young CAD patients more than in those of Old CAD patients and Controls, and this trend was found to be significant by ANOVA ($P = 0.028$). (Figure 2)

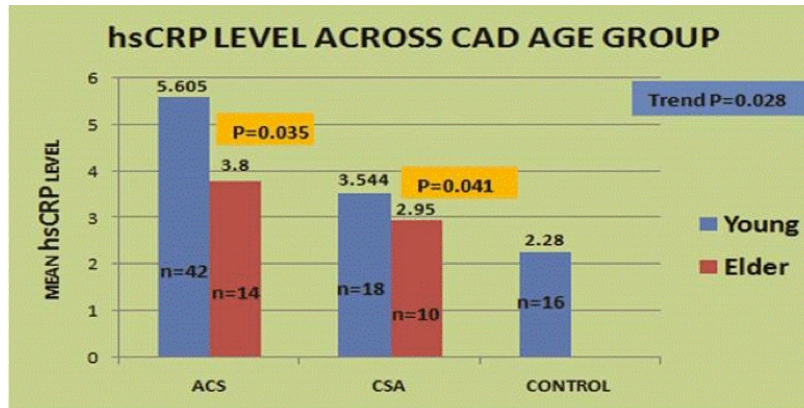


Figure 2: Mean hsCRP across CAD Age Groups

To see the correlation of disease burden, angiographic stenosis score and extent score were compared with the levels of serum hsCRP in young adults with CAD. Mean stenosis scores were 6.35 in the ACS and 3.67 in CSA group of young CAD patients. The Pearson Chi-square

test showed a significant point to point positive correlation between angiographic derived CAD stenosis score (Gensini Score) and levels of inflammatory biomarker – hsCRP ($P < 0.01$, $r = 0.6692$, 95% CI for r - 0.5003 to 0.7891). (Figure 3) The mean extent scores were 36.90 in ACS and

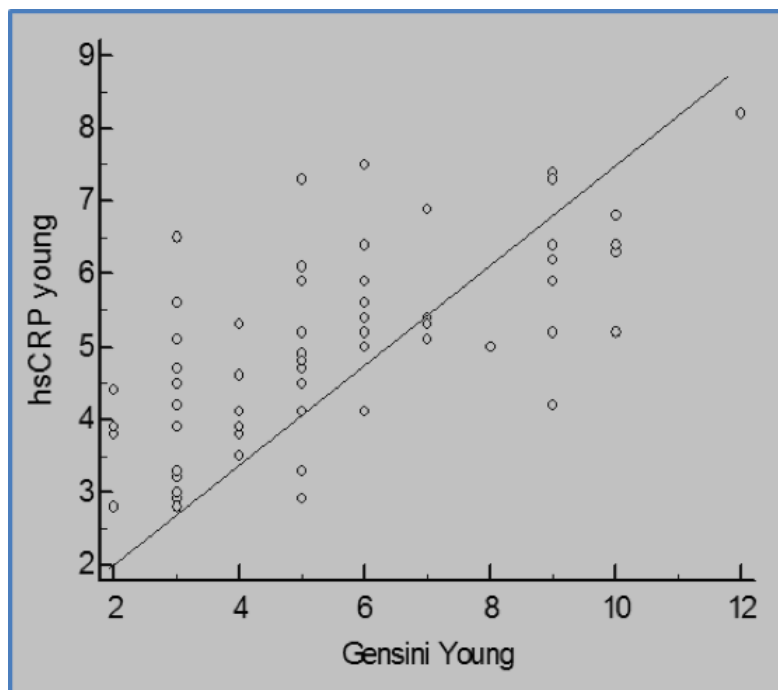


Figure 3: Correlation of hsCRP with CAD Stenosis Score

21.67 in CSA group respectively. Similar to stenosis score, the Pearson Chi-square test showed a significant point to point positive correlation between angiographic derived CAD extent score (Sullivan Score) and serum hsCRP levels ($P < 0.01$, $r = 0.6067$, 95% CI for $r = 0.4170$ to 0.7457).

(Figure 4) Higher hs-CRP levels were associated with higher stenosis and extent scores in young CAD patients. Serum hsCRP is therefore a sensitive indicator of progressive increase in severity of coronary artery stenosis and extent of disease in Young CAD subjects.

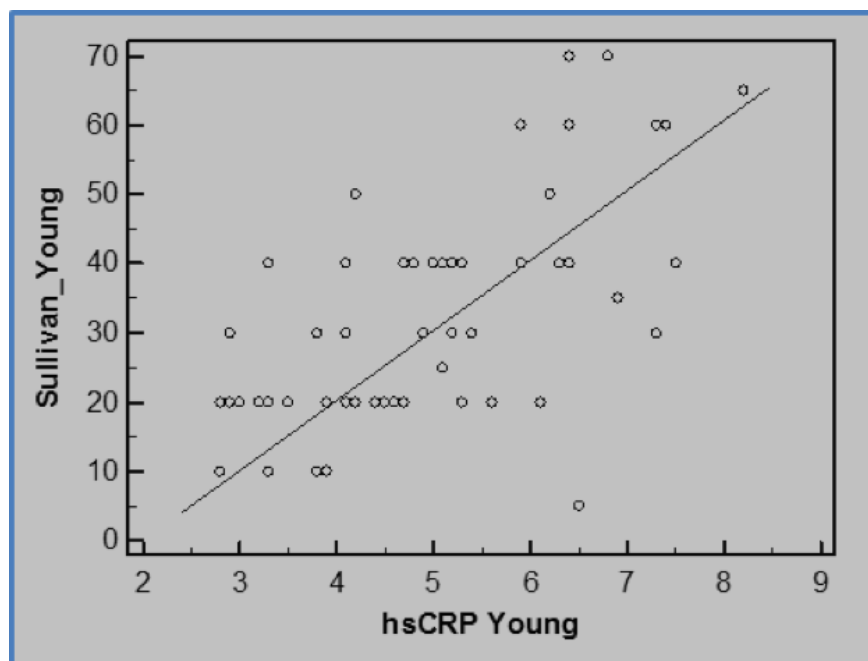


Figure 4: Correlaton of hsCRP With CAD Extent Score

DISCUSSION

Coronary artery disease (CAD) is one of the commonest causes of mortality and morbidity all over the world¹⁰. Coronary artery disease is devastating precisely because an otherwise healthy person in the prime of life may die or become disabled without warning. When the afflicted individual is under the age of 45, the tragic consequences for family, friends, and occupation are particularly catastrophic and unexpected¹¹. The disproportionate rise in prevalence of heart disease among people of Asian Indian origin has been of great interest and these people tend to get MI at a younger age in addition to more complex coronary artery abnormalities¹². Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis.

In recent decades, over 30 epidemiological studies have shown that CRP is associated with cardiovascular risk¹³. In our study, mean hsCRP was significantly elevated in Young CAD patients than in those of Old CAD patients and Controls, and this trend was significant ($P = 0.028$, ANOVA). Also, mean hsCRP was significantly elevated

in both ACS Group ($P = < 0.01$) and CSA (chronic stable angina) Group ($P = 0.02$) of Young CAD patients than in those of Old CAD patients. This important finding indicates the role of vascular inflammation and endothelial dysfunction in the high incidence of CAD in young Indians. This intriguing data suggests the possible involvement of risk factors that are often not considered in typical risk-stratification schemes. Considering the occasional involvement of these factors in older CAD patients, their involvement in the young CAD group should be further elucidated. Klein and Nathan in their editorial comment have also mentioned that the role of inflammation is understudied and it can be assessed by testing levels of systemic inflammatory markers such as high sensitivity C-reactive protein¹⁴.

Correlaton of Inflammation with Angiographic CAD Severity

In the present study, out of 60 Young CAD patients, 26 (43.3%) had single vessel disease (SVD), 24 (40%) had double vessel disease (DVD), 10 (16.7%) had triple vessel disease (TVD). Out of the 24 Old CAD patients, 17 (71%) had SVD, 4 (16.7%) had DVD, 1 (4.2%) had TVD.

(Table 3) The high prevalence of DVD and TVD in the Young CAD (56.7%) versus the Old CAD (20.9%) group has also been reported previously. Klein et al. theorized that two distinct populations exist¹⁵. The more common subgroup is characterized by single-vessel, and often single-stenosis, disease, presumably related to acute plaque

rupture, with an excellent three-year outcome. The favorable prognosis was believed to be related to preserved left ventricular function without multivessel involvement. The less common group has extensive three vessel CAD with “galloping” progression unrestrained by coronary artery bypass graft surgery (CABG) and preventive measures.

Table 3 Distribution of Diseased Vessels

	YOUNG CAD N (%)	OLD CAD N (%)
SVD	26 (43.3%)	17 (71%)
DVD	24 (40%)	4 (16.7%)
TVD	10 (16.7%)	1 (4.2%)

SVD – single vessel disease, DVD – double vessel disease, TVD - triple vessel disease

Pearson Chi-square test shows a significant positive correlation between levels of inflammatory biomarker - hsCRP with angiographic derived CAD stenosis score (Gensini Score) [P <0.01] and extent (Sullivan Score) [P<0.01]. Serum hsCRP may therefore be a sensitive indicator of progressive increase in stenosis severity and extent of coronary artery disease in Young CAD subjects. Similar studies of correlation of inflammation with CAD are available from India, but none documented from Eastern India especially among young CAD patients¹⁶. This is noteworthy as regional differences appear to exist between the type and levels of risk factors present, as evident from studies in North and South Indian CAD patients¹⁷.

Strengths of the Study

Similar correlation of vascular inflammation with CAD has been performed in previous studies, but none documented in India in the population of young CAD. Also, the methodology used in the study was similar to international reports of the same nature, thus making it suitable for purposes of comparison.

Limitations of the Study

It is a cross-sectional study of patients referred for coronary angiography. Such a study design cannot establish causality. It can only establish an association. Hence, any conclusion derived from such a study must be considered preliminary and hypothesis generating rather than hypothesis-proving. Also, studies are needed with a large sample - to delineate the interaction between inflammatory markers like hsCRP and CAD, to investigate whether there is a ‘threshold effect’ of the markers and also whether the markers have any diagnostic or prognostic value, especially in the young.

CONCLUSION

Significantly higher hs-CRP levels are found in spectrum of CAD patients through acute coronary syndrome to chronic stable angina than to patients with normal coronary angiography – indicating a role of inflammation in the process of plaque progression. Serum hs-CRP levels and inflammation have a positive correlation with the disease burden in the young CAD patient. Premature CAD in Young Asian Indians could be partly explained by increased vascular inflammation. Therefore, further studies and interventions to identify & reduce risk factors in an economically and socially relevant section of population of a fast developing country like India is urgently needed.

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Vascular Inflammation and Angiographic Severity of Coronary Artery Disease

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