# Comparison between High SensitiveC-Reactive Protein, Interleukin-6 Levels and White Blood Cell Count in Patients with Coronary Artery Ectasia, Obstructive Coronary Artery Disease and Normal Epicardial Coronary Arteries

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## Abstract

***Background-***Coronary artery ectasia (CAE) is a clinical entity characterized by localized or diffused dilatation of at least 1.5 times that of the normal adjacent segments of the vessel. It was once thought of as a variant of atherosclerosis. The role of inflammation in atherosclerosis is increasingly well known; however, the association between inflammation and CAE has been controversial. The aim of this study was to investigate the possible relationship between leukocyte count and other leukocyte subtypes, the plasma levels of high sensitive C-reactive protein (CRP), and interleukin-6 (IL-6) and the coronary ecstatic process and compare these markers between obstructive coronary artery disease (CAD) patients and normal controls.

***Methods-*** We enrolled 29 patients with CAE and non-obstructive CAD, 29 with obstructive CAD, and 30 normal epicardial coronary according to coronary angiography results. The peripheral blood was taken, and white blood cell count (WBCC) as well as leukocyte subtypes, including neutrophils, lymphocytes, and monocytes cell count, was measured. The plasma levels of high sensitive CRP and IL-6 were determined using the ELISA as well.

***Results-*** A higher number of neutrophils and monocytes were found in the patients with CAE as well as obstructive CAD compared with the normal controls (p value = 0.021). Moreover, levels of plasma high sensitive CRP and IL-6 were also significantly higher in the patients with CAE and in the patients with obstructive CAD than those without CAD (p value < 0.001).

***Conclusion-*** This study demonstrated and expanded prior limited findings showing that significant chronic inflammation may have a relationship with the pathogenesis of CAE, which was associated with not only increased inflammatory markers but also inflammatory cells in the patients with CAE **(*Iranian Heart Journal 2013; 13 (1):11-17).***

**Keywords:** Coronary artery ectasia■ Leukocyte count■ high sensitive CRP■ IL6

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Coronary artery ectasia (CAE) is characterized by localized or diffused dilation of at least 1.5 times that of the normal adjacent segments of the vessel.[1] It is estimated that 50% of CAE cases are related to atherosclerosis, but 20-30% of cases may be due to congenital or inflammatory disease such as the Kawasaki syndrome.[2,3,4] CAE was found in the range of 1.2-4.9% in different studies.[1,5] Its common co-existence with coronary artery disease (CAD) has intensified the idea that CAE is a variant of CAD, but it is not clear why some patients with obstructive CAD develop CAE, whereas most do not.[1,6] It causes adverse coronary events like vasospasm, thrombosis, and dissection.[7] Despite the absence of obvious obstruction, 70% of patients with CAE have established evidence of cardiac ischemia based on cardiac lactate levels during ergometry and atrial pacing.[8] Markis[9] revealed that the underlying histological changes such as diffuse hyalinization and intimal and medial damage were identical to those found in atherosclerotic lesions. Thus, controversy still exists as to the pathogenetic mechanisms that cause CAE.

Inflammation is a central critical feature of atherosclerosis and its clinical manifestations.[10] In recent years, it has been recognized that atherosclerosis is an active, chronic inflammatory process.[11,12,13] Numerous epidemiologic and clinical studies have revealed leukocytes as an independent predictor of future cardiovascular events in patients with CAD and also in healthy persons.[14,15] In addition, a large amount of data has revealed that high sensitive C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation, is elevated among individuals at risk for future cardiovascular events, and adding high sensitive CRP level to standard lipid screening seems to provide an enhanced method to determine vascular risk.[16] Accumulating evidence suggests that CRP might have direct inflammatory roles at different cellular and organic levels.[16] In the group of pro-inflammatory cytokines, interleukin-6 (IL-6) is one of the most important factors and has multiple significant effects on human vascular pathophysiology; in addition, it has been demonstrated that the production of IL-6 is enhanced by monocytes in response to CRP in patients with unstable angina. Moreover, IL-6 is a powerful stimulus for CRP production.[17]

The goal of this study was to examine the total and differential leukocyte counts, plasma high sensitive CRP, and IL-6 in patients with isolated CAE and to compare them with the levels in CAD and normal control subjects. We also aimed to investigate whether increased inflammatory status is associated with the coronary ectatic process.

## Methods

The cases were retrospectively selected from the patients who underwent coronary angiography in Hamedan Ekbatan Hospital between September 2011 and December 2012 due to the presence of typical low threshold angina or positive noninvasive screening tests for myocardial ischemia. A total of 88 cases were enrolled in this study. The first group comprised 29 patients with isolated CAE, the second group consisted of 29 patients with CAD, and the third group encompassed 30 subjects with normal epicardial coronary arteries (NECA).The local Ethics Committee approved the study protocol, and written informed consent was obtained from all the patients prior to enrolment.

The exclusion criteria were patients with acute coronary syndrome, previous myocardial infarction, left ventricular dysfunction, valvular heart disease, uncontrolled hypertension, immunologic or inflammatory disease, sepsis, active local or systemic infection, history of recent infection (< 3 months before the study), untreated thyroid disease, and history of malignancy.

Isolated CAE was defined as localized or diffused non-obstructive lesions of the epicardial coronary arteries with luminal dilatation equal to or greater than 1.5 times that of the normal adjacent segment and without any stenotic lesions by visual assessment of conventional coronary angiography. Obstructive CAD was defined as the angiographically ≥70% stenosis of epicardial coronary artery. Standard selective coronary angiography was performed using the Seldinger Technique and 6F right and left coronary catheters. Blood samples of all the individuals were taken 24 hours after coronary angiography after 12-hour overnight fast from an antecubital vein. Anticoagulated peripheral blood sampling was carried out for the measurement of total and differential blood leukocyte count by an automated hematology analyzer (Cell tack-α, Japan).The plasma was obtained by centrifugation of the blood at 300 rpm for 15 minutes and then stored in two aliquots at -24$^0$ C until assayed. The levels of high sensitivity CRP were determined via the Nephlometry method (Binding Scite, England) and IL-6 was measured using the Eliza immunoassay method (Bioscince, Austria).

## Statistical Analysis

The SPSS software for Windows (version 13.0) was used for all the calculations. The continuous variables are presented as mean ± SD, and the categorical variables are defined as percentages. The Kolmogorov–Smirnov test revealed normal distribution of the quantitative data. The chi-square test was used for the univariate analysis of the categorical variables. The mean values were compared using the one–way ANOVA analysis of variance, followed by the Tukey's Honestly Significant Difference test between the different groups. Statistical significance was defined as a p value < 0.05.

## Results

The baseline clinical characteristics of the subjects with CAE (n=29), with obstructive CAD (n=29), and with angiographically normal controls (n=30) are summarized in Table I.

**Table I- Baseline clinical characteristics of the study groups**

| Variables | CAE (n=29) | CAD (n=29) | NECA (n=30) | P value |
|---|---|---|---|---|
| Age(mean± SD)(yrs) | 60.7±9.1 | 61.7±9.5 | 58.1±9.9 | 0.327 |
| Men/Women | 12/17 | 14/15 | 10/20 | 0.50 |
| Hypertension | 15(52%) | 17(59%) | 13(43%) | 0.42 |
| Diabetes mellitus | 7(24%) | 4(14%) | 6(20%) | 0.60 |
| Hyperlipidemia | 7(24%) | 9(31%) | 9(30%) | 0.84 |
| Cigarette smoking | 5(17%) | 9(31%) | 2(7%) | 0.60 |

CAE, coronary artery ectasia; CAD, coronary artery disease; NECA, normal epicardial coronary arteries; LAD, left anterior descending ; LCX, left circumflex; RCA, right coronary artery

No statistically significant differences were observed between the three groups with respect to age, sex, presence of hypertension, presence of diabetes mellitus, smoking habit, and hyperlipidemia characteristics (p value > 0.05).

The angiographic characteristics of CAE are presented in Table II.

**Table II. Angiographic characteristics of the ectasia**

| Coronary artery ectasia distribution | Number |
|---|---|
| LAD | 26/29(90%) |
| LCX | 23/29(79%) |
| RCA | 22/29(76%) |
| **NO. Of ectatic coronary arteries** | **Number** |
| 1 | 5/29(17%) |
| 2 | 6/29(21%) |
| 3 | 18/29(62%) |

CAE, coronary artery ectasia; CAD, coronary artery disease; NECA, normal epicardial coronary arteries; LAD, left anterior descending ; LCX, left circumflex; RCA, right coronary artery

Ectasia was more prevalent in the left anterior descending coronary artery (LAD) (90%). Also, in most patients, all three coronary arteries were diffusely ecstatic (62%).

The counts of total leukocytes (7745 ± 1102, 7962± 2389, and 6733 ± 1615 cells/mm $^3$ ; p value = 0.021), neutrophils (5383 ± 995, 5452 ± 1941, and 4326 ± 1272 cells/ mm$^3$;p value = 0.005), and monocytes (86 ± 45, 94 ± 58, and 55 ± 33 cells/mm$^3$;p value = 0.005) were significantly different between the CAE, CAD, and NECA groups, respectively.

No significant differences were observed in the count of lymphocytes between the three groups (Table III). The data showed that the count of total leukocytes in the patients with CAE and obstructive CAD compared with those with NECA was high; it was significant in the obstructive group (p value = 0.026) but not significant in the ectatic group (p value = 0.08).The difference between CAD and CAE was also not significant (p value > 0.05).

The count of neutrophils and monocytes, but not lymphocytes, showed a significant association with the presence and severity of CAD and with the presence of isolated CAE. Those values were found to be similar between the CAE and obstructive CAD groups (Table III).

**Table III. Plasma levels of inflammatory cells and markers in the study groups**

| Variables | CAE (n=29) | CAD (n=29) | NECA (n=30) | P value |
|---|---|---|---|---|
| White blood cell count(/mm³) | 7745±1102 | 7962±2389 | 6733±1615 | 0.021 |
| Neutrophils (/mm³) | 5383±995 | 5452±1941 | 4326±1272 | 0.005 |
| Lymphocytes (/mm³) | 2217±511 | 2353±587 | 2296±715 | 0.686 |
| Monocytes (/mm³) | 86±45 | 94±58 | 55±33 | 0.005 |
| Hs-CRP(mg/l) | 4.17±2.42 | 5.23±2.34 | 2.12±.8 | <0.001 |
| IL-6(pg/dl) | 7.31±.86 | 7.46±1.47 | 5.7±1.17 | <0.001 |

CAE, coronary artery ectasia; CAD, coronary artery disease; NECA, normal epicardial coronary arteries; Hs-CRP, high-sensitive C- reactive protein ; IL-6, interleukin-6

As is demonstrated in Table 3, the plasma high sensitive CRP levels (4.17± 2.42 mg/1, 5.23± 2.34 mg/1, and 2.12± 0.8; p value < 0.001) were significantly different between the CAE, CAD, and NECA groups, respectively. The plasma high sensitive CRP levels were higher in the patients with CAE and the ones with obstructive CAD than those in the subjects with NECA. The difference between CAD and CAE was also not significant (p value = 0.109). In addition, the pattern of plasma IL-6 levels was also similar to that of high sensitive CRP levels. Plasma IL-6 levels were detected to be significantly higher in the patients with CAE and the ones with obstructive CAD than in the subjects with angiographically normal coronary arteries (7.31 ± 0.86 pg/dl, 7.46 ± 1.47 pg/dl, and 5.7 ± 1. 17 pg/dl; p value < 0.001), respectively. The difference between CAD and CAE was also not significant (p value = 0.879).

## Discussion

The fundamental pathogenesis of CAE is until now unknown. The role of inflammation in atherosclerosis is increasingly well known. However, the association between inflammation and CAE has been inadequate and controversial,[16] The main finding of this study is that in patients with CAE, similar to patients with obstructive CAD, the count of blood circulating inflammatory cells such as neutrophils and monocytes and plasma levels of inflammatory markers such as high sensitive CRP and IL-6 are significantly higher than those with angiographically normal epicardial coronary arteries. Also, the count of total leukocytes was higher in the patients with CAE than in the subjects with normal coronary arteries; the difference was, however, not statistically significant.

CAE was found in the range of 1.2-4.9% in different studies.[1,5] It causes adverse coronary events like vasospasm, dissection, and thrombosis.[7, 16] In some studies, coronary aneurysms have been strongly related with an

increased risk of myocardial infarction.[18,19] Recent investigations have revealed that CAE is associated with inflammatory response, presenting as elevated inflammatory cytokines and differential leukocyte. Kocaman[10] reported that the CAE patients had significantly higher leukocytes and subtype counts, including neutrophils and monocytes, than the non-obstructive CAD patients and normal control subjects; nevertheless, there was no significant difference between the patients with CAD and CAE.

Turhan[20] assessed plasma CRP levels, a specific marker of inflammation, in 32 patients with isolated CAE and compared the results with those of 32 patients with obstructive CAD and 30 subjects with angiographically normal coronary arteries and showed that increased CRP levels were found in the CAE patients only. In contrast, Finkelstein[21] found that there were no differences in the levels of CRP between the CAE and CAD as well as normal control subjects. Tokgozoglu[22] examined 43 patients with CAE and showed that serum IL-6 levels were significantly higher in the patients with CAE than in the normal controls. Yilmas[23] showed that patients with isolated CAE had elevated levels of plasma soluble intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1(VCAM-1), and E-selection in comparison to the patients with obstructive CAD and subjects with normal coronary arteries, suggesting the presence of a more severe and extensive chronic inflammation in the coronary circulation in these patients. Turhan[24] demonstrated raised levels of ICAM-1 and VCAM-1 in the patients with CAE and obstructive CAD plus CAE compared with subjects with normal coronary arteries and obstructive CAD. The results obtained in our study strengthen and extend previous limited studies and show that not only plasma high sensitive CRP and IL-6 levels but also elevated circulating inflammatory cells are associated with the progress of CAE.

Although the mechanism that causes CAE is not clearly understood, it is important to evaluate the risk factors in these patients, which could influence the manifestation of this situation. A large number of studies have shown that atherosclerosis is an inflammatory disease. The inflammatory process exists in the earliest phase of atherosclerosis; increased infiltration of leukocytes may lead to vulnerable plaque formation and acute plaque rupture, leading to acute coronary syndrome.[10] Leukocytosis influences atherosclerosis via pathologic mechanisms such as the mediation of inflammation and oxidative and proteolytic damage to the endothelial cells.[15]Regardless of the mechanism responsible for CAE formation, it is developed primarily from thinning and/or destruction of the media. CAE may arise during the development of coronary atherosclerosis. On the other hand, the ectatic process may also be independent from the atherosclerotic process, because it can be found isolated in coronary and other vascular system.[25] Certain coronary plaques do not diminish the luminal size, most probably because of the expansion of the media and external elastic membrane during atheroma formation; this is known as arterial remodeling.[26] Expansive remodeling is related with unstable clinical presentation and inflammatory reaction.[25] Consequently, CAE is not an innocent clinical condition; it may cause increased cardiovascular events, possibly via slow coronary blood flow, vasospasm, dissection, microemboli, or thrombosis.[10]

In another study, statin and angiotensin-converting enzyme inhibitors were used to suppress the CRP levels in CAE, and it was achieved within 3 months of treatment.[27] Combined treatment with ASA and statin may be the best option.[10]

## Conclusion

To the best of our knowledge, this is the first study of its kind to assess the inflammatory

status in the CAE patients in our country. The results chime in with those of previous studies and underscore the notion that inflammatory cells and markers are significantly different between patients with CAE and those with normal epicardial coronary arteries. However, in contrast to some previous studies, this difference was not observed between these patients and those with obstructive coronary arteries. We believe that further studies are needed to elucidate the role of inflammation in CAE. Perhaps further studies would lead to effective treatment options to improve this clinical status.

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**Conflict of Interest**
No conflicts of interest have been claimed by the authors.

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