

## Research Article

# Role of Inflammatory Markers in Patients with Coronary Artery Ectasia versus Patients with Obstructive Coronary Artery Disease

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## Abstract

**Objective:** The aim of the study is to compare between Eosinophilic Count (EC), Mean Platelet Volume, (MPV), Neutrophil/Lymphocyte Ratio (NLR) and High Sensitive CRP (HS-CRP) level in patients with coronary artery ectasia versus patients with obstructive coronary artery disease.

**Methods:** 150 patients underwent diagnostic coronary angiography in cardiology departments of Mahalla cardiology center and Benha University hospitals, divided into three groups, 50 patients with Coronary Artery Ectasia (CAE), 50 patients with Obstructive Coronary Artery Disease (O-CAD) and 50 patients as a control group.

**Results:** All parameters were found to be significantly increased when comparing patients have CAE or O-CAD with the controls ( $P<0.001$ ). Plasma levels of EC and HS-CRP were significantly higher in CAE patients compared with O-CAD patients ( $0.202 \pm 0.075$ ,  $0.126 \pm 0.031/\text{nl}$ ,  $P<0.001$ ), ( $2.45 \pm 0.5$ ,  $2.23 \pm 0.42 \text{ mg/l}$ ,  $P=0.045$ ) respectively. Meanwhile levels of MPV and NLR were insignificant in CAE patients compared to O-CAD patients ( $7.354 \pm 0.623$ ,  $7.338 \pm 0.486 \text{ mL}$ ,  $P=0.642$ ), ( $2.857 \pm 0.88$ ,  $2.667 \pm 0.569$ ,  $P=0.222$ ) respectively.

**Conclusion:** This study has revealed a relationship between plasma EC and HS-CRP and Coronary Artery Ectasia (CAE) in comparison to patients with Obstructive Coronary Artery Disease (O-CAD). These results confirm that CAE is a more severe inflammatory process than O-CAD.

**Keywords:** Angiography; Coronary Ectasia; Eosinophils; High Sensitive CRP; Inflammatory Markers

## Abbreviations

|        |   |                                 |                          |           |
|--------|---|---------------------------------|--------------------------|-----------|
| AUROC  | : | Area Under Characteristic curve | Under Receiver Operating | Operating |
| CAD    | : | Coronary Artery Disease         |                          |           |
| CAE    | : | Coronary Artery Ectasia         |                          |           |
| CI     | : | Confidence Interval             |                          |           |
| EC     | : | Eosinophilic Count              |                          |           |
| HS-CRP | : | High Sensitive CRP              |                          |           |
| MPV    | : | Mean Platelet Volume            |                          |           |
| NLR    | : | Neutrophil/Lymphocyte           | Neutrophil               |           |

|           |   |                                     |  |
|-----------|---|-------------------------------------|--|
| Ratio     |   |                                     |  |
| NPV       | : | Negative Predictive Value           |  |
| OR        | : | Odds Ratio                          |  |
| O-CAD     | : | Obstructive Coronary Artery Disease |  |
| PPV       | : | Positive Predictive Value           |  |
| ROC curve | : | Receiver Operating Characteristic   |  |
| curve     |   |                                     |  |
| SN        | : | Sensitivity                         |  |
| SP        | : | Specificity                         |  |

## Introduction

Coronary Artery Ectasia (CAE) is characterized by an abnormal dilatation of the coronary arteries, which is a variant of

Coronary Artery Disease (CAD) [1]. In general, CAE is considered to be a different form of vascular remodeling in response to atherosclerosis; however, the underlying mechanisms responsible for ectasia formation are clearly unknown [2].

Therefore, determination of the factors associated with the presence and severity of CAE may have a salutary influence on the management of these patients. Previous studies have demonstrated that inflammation, neuro-hormonal process and cardiovascular risk factors are associated with development of CAE. Although it has been suggested that CAE is a commonly a variant of O-CAD, a definitive link between atherosclerosis and ectasia has not been confirmed [3]. Based on the findings obtained from previous studies it was suggested that, a more severe inflammation could be involved in the pathogenesis of CAE [4]. In addition, C reactive protein (CRP) is a sensitive marker of systemic inflammation and the elevation of systemic and local levels of this inflammatory marker has been associated with an increased risk for cardiovascular disease [5,6].

This study will be performed on the hypothesis that a more severe inflammation might be involved in development of isolated CAE compared to obstructive CAD (O-CAD).

## Methods

### Study Population

Among patients with angina pectoris undergoing angiographic procedures, 150 patients were prospectively selected for this study. On the basis of angiographic findings, they were divided into three groups; 50 patients with isolated CAE, 50 patients with obstructive CAD and age-matched, sex-matched, 50 controls with normal coronary arteries. Medical history, atherosclerotic risk factors, and medications were interrogated on physical examination. Blood samples were obtained at least 7 days after coronary angiography to exclude possible effect of angiography on inflammatory situation. Non-inclusion criteria were as follows: acute coronary syndromes, known aortic aneurysms, hematological disorders, acute/chronic infectious diseases, hepatitis or previously known inflammatory/autoimmune disorders, acute/chronic renal failure, documented cancer, use of steroids, and renin-angiotensin-aldosterone system blockers. All patients were provided informed consent for participation in this study.

### Assay of Inflammatory Markers

Blood samples were drawn into tubes including EDTA after an 8-h fasting period in the morning with minimal trauma from antecubital vein. Plasmas were separated by centrifugation at 3000g for 10 min and then stored at -70°C.

Absolute cell counts and mean platelet volume were used in this analysis. C-reactive protein was estimated. Total lipid profile and fasting glucose were also measured.

### Angiographic Evaluation

Coronary angiography was obtained in right and left anterior oblique projection with caudal and cranial angulations for the left and right coronary system. Images were recorded in digital format and stored for later analyses. Right anterior oblique view was considered to evaluate the ectasia for the left coronary system and left anterior oblique view for the right coronary artery. Evaluations were visually performed by two experienced angiographers. The vessel diameter was calculated quantitatively in case of presence of conflict about CAE.

Each major coronary artery was subdivided into proximal, middle, and distal segments. Coronary ectasia was defined as a dilation exceeding the 1.5-fold of normal diameters in major coronary arteries [1,2]. If no adjacent normal segment could be identified, the mean diameter of the corresponding segment in the control group was considered as normal value. A luminal narrowing greater than 50% in the coronary artery was considered as obstructive CAD. Absence of any atherosclerotic plaques was regarded as normal coronary artery. Patients with concomitant obstructive and ectatic lesions were not included in this study.

### Statistical Analysis

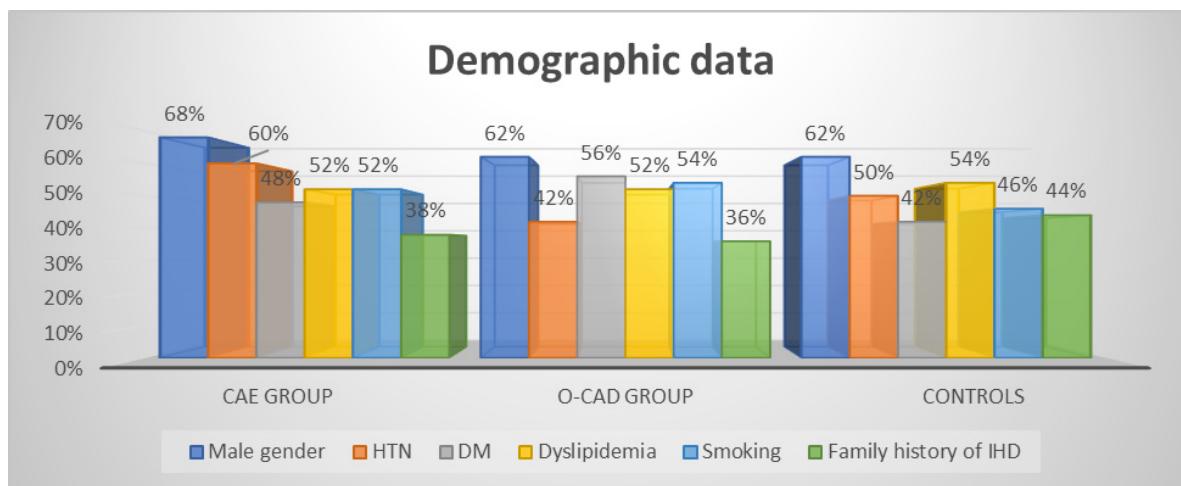
Continuous variables were presented as mean  $\pm$  SD and categorical variables as number (%). Comparisons between the groups were performed with Student's t-test, Mann-Whitney U test and Fisher's exact test as appropriate. Kruskal Wallis test was used for relationship between the severity of CAE and inflammatory markers. Receiver operating characteristics analysis was used to estimate cut-points for EC, MPV, NLR and HS-CRP to identify CAE patients in the study population. A P value of less than 0.05 was considered significant. All analyses were made by using SPSS 11.0

## Results

| Variables             | CAE group<br>(n=50) | O-CAD group<br>(n=50) | Control group<br>(n=50) | P values |       |       |
|-----------------------|---------------------|-----------------------|-------------------------|----------|-------|-------|
|                       |                     |                       |                         | P1       | P2    | P3    |
| Mean age              | 57.7 ± 5.9          | 58.2 ± 5.9            | 58.6 ± 5.2              | 0.355    | 0.709 | 0.602 |
| Male/Female           | 34/16               | 31/19                 | 31/19                   | 0.529    | 0.529 | 1.00  |
| Risk factors:         |                     |                       |                         |          |       |       |
| Hypertension          | 30 (60%)            | 21 (42%)              | 25 (50%)                | 0.315    | 0.072 | 0.422 |
| Diabetes              | 24 (48%)            | 28 (56%)              | 21 (42%)                | 0.546    | 0.423 | 0.161 |
| Dyslipidemia          | 26 (52%)            | 26 (52%)              | 27 (54%)                | 0.841    | 1.00  | 0.841 |
| Smoking               | 26 (52%)            | 27 (54%)              | 23 (46%)                | 0.548    | 0.841 | 0.424 |
| Family history of CAD | 19 (38%)            | 18 (36%)              | 22 (44%)                | 0.542    | 0.836 | 0.414 |

P1: CAE versus controls; P2: CAE versus O-CAD; P3: O-CAD versus controls.  
Variables were presented mean ± SD, and n (%).  
O-CAD: Obstructive Coronary Artery Disease; CAE: Coronary Artery Ectasia.

**Table 1:** Baseline clinical characteristics of the study population.



**Figure 1:** Demographic data of the study groups.

| Variables    | CAE group<br>(n=50) | O-CAD group<br>(n=50) | Controls<br>(n=50) | P values |        |        |
|--------------|---------------------|-----------------------|--------------------|----------|--------|--------|
|              |                     |                       |                    | P1       | P2     | P3     |
| EC /nl       | 0.202 ± 0.075       | 0.126 ± 0.031         | 0.066 ± 0.013      | <0.001   | <0.001 | <0.001 |
| NLR          | 2.857 ± 0.88        | 2.667 ± 0.569         | 1.117 ± 0.395      | <0.001   | 0.222  | <0.001 |
| MPV fL       | 7.354 ± 0.623       | 7.338 ± 0.486         | 5.409 ± 0.499      | <0.001   | 0.642  | <0.001 |
| Hs-CRP mg/dl | 2.45 ± 0.5          | 2.23 ± 0.42           | 0.68 ± 0.15        | <0.001   | 0.045  | <0.001 |

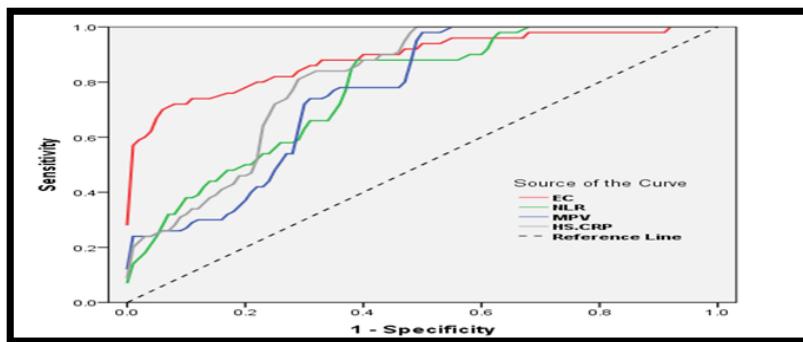
P1 = CAE group versus controls; P2 = CAE group versus O-CAD group; P3 = O-CAD group versus controls.  
O-CAD: Obstructive Coronary Artery Disease; CAE: Coronary Artery Ectasia, HS-CRP: High-Sensitive C-Reactive Protein; EC: Eosinophil Count; NLR: Neutrophil/Lymphocyte Ratio; MPV: Mean Platelet Volume.

**Table 2:** Inflammatory markers levels of the study groups.

| Cut-off value  | Sensitivity % | Specificity % | PPV % | NPV % | Accuracy | AUROC | p-value     |
|----------------|---------------|---------------|-------|-------|----------|-------|-------------|
| EC > 0.1375    | 80%           | 80%           | 66.7% | 88.9% | 80%      | 0.888 | <0.001 (HS) |
| NLR > 1.9775   | 88%           | 60%           | 52.4% | 90.9% | 69.3%    | 0.771 | <0.001 (HS) |
| MPV > 7.0115   | 70%           | 71%           | 54.7% | 82.6% | 70.7%    | 0.763 | <0.001 (HS) |
| HS-CRP > 1.925 | 82%           | 70%           | 58.6% | 88.6% | 74%      | 0.808 | <0.001 (HS) |

ROC curve: Receiver Operating Characteristic curve; SN: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUROC: Area Under Receiver Operating Characteristic curve.

**Table 3:** Inflammatory markers as predictors for CAE; ROC curve analysis in reference to controls.



**Figure 2:** ROC curve analysis regarding CAE.

In the receiver operating characteristics analysis, EC levels greater than 0.1375/nl identified CAE patients with 80% sensitivity and 80% specificity (Area Under Curve=0.88, P<0.001). Similarly, hs-CRP levels greater than 1.925 mg/dl estimated the patients with 82% sensitivity and 70% specificity (Area Under Curve=0.808, P<0.001).

| Study groups a | Inflammatory markers | Intercept | Std. Error | Wald   | Degree of freedom | Sig.  | Odds ratio       | 95% Confidence Interval for Odds ratio |             |
|----------------|----------------------|-----------|------------|--------|-------------------|-------|------------------|--|-------------|
|                |                      |           |            |        |                   |       |                  | Lower Bound                            | Upper Bound |
| CAE            | Constant             | -74.516   | 624.132    | .014   | 1                 | .905  |                  |  |             |
|                | EC                   | 25.369    | 4702.258   | .000   | 1                 | .996  | 104113564502.584 | .000                                   | . b         |
|                | NLR                  | 3.052     | 378.475    | .000   | 1                 | .994  | 21.150           | .000                                   | . b         |
|                | MPV                  | 5.273     | .472       | 124.55 | 1                 | .000  | 195.017          | 77.249                                 | 492.325     |
|                | HS-CRP               | 22.184    | 527.589    | .002   | 1                 | .966  | 4307382465.904   | .000                                   | . b         |
| O-CAD          | Constant             | -63.837   | 624.118    | .010   | 1                 | .919  |                  |  |             |
|                | EC                   | .958      | 4702.255   | .000   | 1                 | 1.000 | 2.607            | .000                                   | . b         |
|                | NLR                  | 2.672     | 378.475    | .000   | 1                 | .994  | 14.469           | .000                                   | . b         |
|                | MPV                  | 4.779     | .000       | .      | 1                 | .     | 118.969          | 118.969                                | 118.969     |
|                | HS-CRP               | 21.252    | 527.588    | .002   | 1                 | .968  | 1696494334.279   | .000                                   | . b         |

a. The reference category is: Normal CA group.  
b. Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

**Table 4:** Multinomial logistic regression analysis for inflammatory markers for CAE and O-CAD.

A multinomial logistic regression model was performed for the tested inflammatory markers to determine the likelihood that participants would have CAE or O-CAD. The result showed that MPV is an independent predictor for CAE [Odds Ratio (OR) =195.017; 95% Confidence Interval (C.I) = 77.249 – 492.325; p<0.001].

## Discussion

Coronary Artery Ectasia (CAE) has been defined as localized or diffuse non-obstructive lesions of the epicardial coronary arteries, with a luminal dilation  $\geq$  1.5 times normal of the adjacent segments or vessel diameter. Isolated CAE has been defined as CAE without significant coronary artery stenosis. This abnormal dilatation of coronary arteries can cause angina pectoris and even myocardial infarction due to vasospasm, dissection or thrombus in patients without coronary artery disease [1,7].

Therefore, determination of the factors associated with the presence and severity of CAE may have a salutary influence on the management of these patients[8]. Previous studies have demonstrated that inflammation, neuro hormonal process and cardiovascular risk factors are associated with development of CAE. Although it has been suggested that CAE is a commonly a variant of O-CAD, a definitive link between atherosclerosis and ectasia has not been confirmed [3,8].

Plasma esinophilic Count (EC) was found to be significantly higher in patients with isolated CAE compared to both patients with O-CAD or controls (p value < 0.001).

Puri R et al. and Freeman et al., reported in previous studies that eosinophilic vasculitis with medial necrosis has been identified at autopsy in otherwise healthy individuals with spontaneous coronary dissection or rupture[9]. It has therefore been proposed that cytotoxic substances released from perivascular eosinophils may result in direct medial destruction, predisposing to aneurysmal formation or spontaneous intimal dissection and sudden cardiac death [10-19]. Also,Moosbauer et al. and Khoury et al., reported in their studies that eosinophils are equipped with several granule- associated molecules which play a role in the occurrence of thrombosis and vascular injury. Also eosinophils generate an increased tendency to thrombosis through leukocyte, platelet stimulation and release of tissue factor [20,21].

Neutrophil to Lymphocyte Ratio (NLR) showed significant increase in CAE and O-CAD groups in comparison to controls (p value < 0.001). Previously, Işık et al., stated in their study that NLR is a readily available clinical laboratory value that is associated with the presence of isolated CAE [3].Also,Sarli et al., stated that NLR was significantly higher in patients with CAE than in patients with normal coronaries [22].

According to MPV there was significant difference between the CAE and O-CAD in comparison to controls [p value < 0.001].

The results of Sen et al., confirmed that patients with CAE have higher MPVs than control subjects with normal coronary angiograms. The increased MPV values may indicate the altered platelet reactivity and aggregation in patients with CAE [23,24].

With reference to HS-CRP, in present study, the mean level of HS-CRP in CAE, O-CAD and control groups was (2.45  $\pm$  0.5, 2.23  $\pm$  0.42 and 0.68  $\pm$  0.15 respectively) with high significant increase in patients of CAE and O-CAD compared to controls [p value < 0.001]. Also there was a significant difference in serum level of HS- CRP between patients with isolated CAE when compared to patients with O-CAD [p value = 0.045]. These results were consistent with the results of Wang et al., study which reported that HS- CRP levels were significantly higher in patients with isolated CAE, suggesting that more severe inflammation may be involved in CAE [25,26].

## Conclusion

As a result, current study has revealed a clear relationship between plasma EC and HS-CRP and Coronary Artery Ectasia (CAE) when compared to patients with obstructive coronary artery disease or controls. This was in context with the hypothesis of CAE as a more severe inflammatory process than O-CAD. In spite of insignificant differences for NLR or MPV in patients with CAE when compared to patients with O-CAD, MPV was an independent predictor for CAE.

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