Original Article

Neutrophil to Lymphocyte Ratio as an Inflammatory Marker in Patients with Lone Coronary Artery Ectasia in Comparison with Stenotic Coronary Artery Disease

Younes Nozari[1], Seyed Ali Mousavi[1], Akbar Shafiee[1,2]

[1]Tehran Heart Center, Tehran University of Medical Sciences, [2]Department of Community Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Coronary artery ectasia (CAE) is an uncommon but known finding in coronary angiography. We compared the neutrophil to lymphocyte ratio in patients with sole CAE and coronary artery disease (CAD) patients as well as normal coronary individuals who presented to our center. **Methods:** In this case-control study, we compared patients with lone coronary ectasia with two other groups: patients with CAD and normal coronary individuals. Demographic and clinical data of the ectatic patients were retrieved from the databank of our center and all variables, particularly neutrophil to lymphocyte ratio compared between the study groups. **Results:** A total of 233 patients with coronary ectasia met our criteria and were compared to 433 stenotic CAD patients and 466 normal coronary individuals. The neutrophil to lymphocyte ratio was significantly lower in the normal coronary individuals ($P < 0.001$). However, there was no significant difference between the coronary ectasia group and the CAD group. This difference was significantly lower in the normal coronary group ($P < 0.001$), while no difference was observed between the ectasia and the CAD group ($P = 0.127$). **Conclusion:** Higher neutrophil to lymphocyte ratio was present in patients with CAE and CAD patients than the normal coronary individuals.

Keywords: Coronary angiography, coronary artery disease, coronary artery ectasia, inflammation, neutrophil to lymphocyte ratio

Introduction

Coronary artery ectasia (CAE) is an uncommon but known finding in coronary angiography. It manifests by an unusual dilatation of the coronary artery lumen that exceeds the largest diameter of an adjacent normal artery more than 1.5-fold.[1,2] The incidence of this finding in coronary angiography is between 0.3% and 4.9%, and it is seen more frequently in men.[3] Etiology of CAE is not well understood yet, but atherosclerosis is considered as the main responsible factor in the adults, and Kawasaki disease is the main cause in children and adolescents.[4-6] Histopathologic studies have shown similarities between CAE and atherosclerosis; however, there are many patients that develop CAE without any evidence of coronary artery disease (CAD) and atherosclerosis.[7,8]

Both atherosclerosis and ectasia formation are considered as the result of inflammatory processes.[9,10] Moreover, CAE was associated with higher levels of gamma-glutamyltransferase, C-reactive protein (CRP), and vascular endothelial growth factor as well as overexpression of matrix metalloproteinases and endogenous nitric oxide.[6,11-14] This signifies the high extent of the inflammation that may result in ectasia.

Neutrophil to lymphocyte ratio is one of the diagnostic and prognostic markers for CAD.[15,16] Due to the inflammatory process of CAE, it is probable that neutrophil to lymphocyte ratio can also be used to determine patients with CAE. In the present study, we compared the neutrophil to lymphocyte ratio in patients with sole CAE and CAD patients as well as normal coronary individuals who presented to our center.

Address for correspondence: Dr. Akbar Shafiee, Department of Cardiovascular Research, Tehran Heart Center, North Kargar Ave, 1411713138, Tehran, Iran.
E-mail: dr_shafiee@alborzi.com

Access this article online

Quick Response Code:

Website: http://www.rcvmonline.com/

DOI: 10.4103/rcm.rcm_32_17

How to cite this article: Nozari Y, Mousavi SA, Shafiee A. Neutrophil to lymphocyte ratio as an inflammatory marker in patients with lone coronary artery ectasia in comparison with stenotic coronary artery disease. Res Cardiovasc Med 2018;7:78-81.

Methods

In this case–control study, we compared patients with lone coronary ectasia who presented to our center between 2004 and 2014 with two other groups: patients with CAD and a group of normal coronary individuals who were candidate for coronary angiography. Our inclusion criteria were (1) age above 18 years and (2) otherwise normal coronary artery structure for the ectatic patients and normal coronary structure for the normal coronary control group. The exclusion criteria included (1) history of coronary artery bypass graft or valvular heart surgery; (2) history of percutaneous coronary intervention; (3) presence of active infection at the time of coronary angiography; (4) history of inflammatory or autoimmune disease; (5) renal insufficiency; (6) hepatic failure or cirrhosis; (7) malignancy; (8) chronic obstructive pulmonary disease; (9) previous myocardial infarction; (10) heart failure or ejection fraction below 50%; (11) hematologic disorders; (12) moderate-to-severe valvular heart disease (either stenosis or regurgitation); and (13) leukocytosis >12,000/mm^3.

Demographic and clinical data of the ectatic patients were retrieved from the databank of our center and reviewed for the inclusion and exclusion criteria. In the next step, their coronary angiography film was reviewed to make sure about the presence and location of the ectasia. For every ectatic patient, 4 controls were selected from the Tehran Heart Center database of coronary angiography using propensity score matching method (matched for age and sex). Two of them were selected from the CAD patients and the other two from the normal coronary individuals.

Demographic characteristics (age and sex), physiologic data (height, weight, blood pressure, and heart rate), history of cardiovascular risk factors, i.e., diabetes mellitus, hypertension, dyslipidemia, family history of CAD, smoking, and opium abuse, drug history, results of the coronary angiography, and laboratory measurements, particularly the results of the complete blood count, were retrieved from our databank and entered in the study's dataset after data cleaning.

As the main study variable, neutrophil to lymphocyte ratio was calculated for all of the participants, and finally, all the study variables were compared among the three study groups.

Statistical analysis

Categorical variables were expressed as frequency and percentage and were compared among the groups using Chi-square test. Continuous variables were described with mean and standard deviation or with median and 25th and 75th percentiles for skewed data and were compared among the groups using one-way analysis of variance or Kruskal–Wallis test. Multiple comparisons based on ranks were used to determine the group difference of neutrophil to lymphocyte ratio. A linear regression model was applied to evaluate the association between logarithm of neutrophil to lymphocyte ratio with groups, adjusting for detected potential confounders. $P < 0.05$ was considered as statistically significant. The statistical analysis was performed using IBM SPSS statistics for windows version 22.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered as statistically significant. The statistical analysis was performed using IBM SPSS statistics for windows version 23.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 233 patients with coronary ectasia met our criteria and were compared to 433 CAD patients and 466 normal coronary individuals. Comparison of the baseline characteristics among the study groups is given in Table 1. In brief, frequency of the smokers and history of CAD were significantly higher in the CAD group ($P = 0.031$ and $P = 0.04$, respectively). Hemoglobin level was also higher in the coronary ectasia group ($P = 0.001$).

As shown in Table 2, comparison of the angiographic characteristics was not different between the groups. The most common affected vessel, both in ectasia and CAD, was the right coronary artery.

The linear regression model showed that the neutrophil to lymphocyte ratio was significantly lower in the normal coronary individuals ($P < 0.001$). However, there was no significant difference between the coronary ectasia group and the CAD group.

After adjustment for the confounding variables, including diabetes, family history of CAD, smoking, high-density lipoprotein levels, creatinine, body mass index, ejection fraction, hemoglobin, mean platelet volume, and mean corpuscular hemoglobin, the neutrophil to lymphocyte ratio remained significantly lower in the normal coronary group ($P < 0.001$), despite no difference between the ectasia and the CAD group ($P = 0.127$).

Discussion

In the present study, we observed a higher neutrophil to lymphocyte ratio in patients with CAE as compared to normal coronary individuals. However, the difference of the neutrophil to lymphocyte ratio between the ectatic patients and the CAD patients was not significant.

Despite several histopathologic similarities between coronary ectasia and atherosclerosis, the exact link between these two conditions has not been confirmed yet. However, it was shown that inflammation plays an evident role in the formation of ectasia as well as atherosclerosis. High levels of adhesion molecules, such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, were observed in ectatic patients as compared with CAD patients.[17,18] Moreover, elevated CRP levels were reported in patients with isolated coronary ectasia that suggests extensive inflammation in patients with ectasia.[19] A temporal association between circulating proteolytic, inflammatory, and neurohormonal markers in patients with coronary ectasia was observed in another study.[20] As a newer marker, neutrophil

Table 1: Comparison of the general characteristics between the study groups

Characteristics	Ectasia (n=233)	CAD (n=466)	Normal controls (n=466)	P
Age (year)	57.6±10.8	57.8±9.9	57.1±10.0	0.447
Male gender, *n* (%)	165 (70.8)	328 (70.4)	330 (70.8)	0.988
BMI (kg/m^2)	29.1±4.6	28.3±4.4	28.4±4.5	0.078
Hypertension, *n* (%)	123 (52.8)	263 (56.4)	258 (55.4)	0.658
Diabetes mellitus, *n* (%)	44 (18.9)	79 (17.0)	88 (18.9)	0.704
Dyslipidemia, *n* (%)	144 (61.8)	300 (64.4)	318 (68.2)	0.201
Smoking, *n* (%)	51 (21.9)	116 (24.9)	83 (17.8)	0.031
Opium, *n* (%)	25 (10.7)	65 (13.9)	45 (9.7)	0.111
Family history of CAD, *n* (%)	43 (18.5)	104 (22.3)	65 (13.9)	0.004
Total cholesterol (mg/dl)	175.1±41.1	181.1±45.0	180.5±43.7	0.208
LDL (mg/dl)	109.0±36.2	111.9±37.6	110.5±38.1	0.634
HDL (mg/dl)	41.6±10.5	41.4±10.3	42.9±10.4	0.078
Triglyceride (mg/dl)	135.5 (100-185)	138 (104.5-195.5)	142 (102-199.5)	0.182
Fasting blood sugar (mg/dl)	106.2±23.4	111.1±36.4	111.2±37.2	0.155
Creatinine (mg/dl)	0.93±0.21	0.94±0.20	0.90±0.21	0.005
WBC	7624±1773	7699±1805	7505±1794	0.262
Hemoglobin (g/dl)	15.1±1.5	14.6±1.6	14.8±1.6	0.001
MCV	87.2±5.4	86.4±5.9	86.0±5.9	0.039
RDW	13.2±1.0	13.2±1.2	13.3±1.2	0.216
PDW	12.7±1.8	12.5±1.9	12.5±1.9	0.58
MPV	9.7±0.9	9.6±0.9	9.6±0.9	0.213
Neutrophil/lymphocyte	2 (1.5-2.7)	2 (1.6-2.8)	1.7 (1.3-2.3)	<0.001
Ejection fraction (%)	57.3±3.1	55.7±4.2	55.8±4.1	<0.001

MCV: Mean corpuscular volume, MPV: Mean platelet volume, PDW: Platelet distribution wide, RDW: Red cell distribution wide, BMI: Body mass index, CAD: Coronary artery disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell

Table 2: Comparison of the angiographic characteristics between the study groups

Characteristics	Ectasia (n=233)	CAD (n=466)	P
Vessel			
LAD	41 (17.6)	77 (16.5)	0.866
RCA	49 (21.0)	107 (23.0)	
LCX	25 (10.7)	50 (10.7)	
LAD + RCA	31 (13.3)	70 (15.0)	
LAD + LCX	27 (11.6)	50 (10.7)	
RCA + LCX	13 (5.6)	16 (3.4)	
LAD + RCA + LCX	47 (20.2)	96 (20.6)	

LAD: Left anterior descending, RCA: Right coronary artery, LCX: Left circumflex artery, CAD: Coronary artery disease

to lymphocyte ratio has been used to show the inflammatory pathogenesis and severity of CAD in various studies.[21,22]

Due to histopathologic similarities in the coronary ectasia and CAD, it has been tested whether neutrophil to lymphocyte ratio is elevated in ectatic patients and the results approved this hypothesis. Ayhan *et al*. have shown in a study that neutrophil to lymphocyte ratio was significantly higher in the coronary ectasia group compared with normal coronary control group.[23] A similar study also showed association of neutrophil to lymphocyte ratio with the presence of isolated CAE.[24] However, the populations of both studies were rather small, and they did not have a control group with CAD. In another study, Balta *et al*. compared the level of neutrophil to lymphocyte ratio between patients with CAE, those with newly diagnosed CAD, and those with a normal coronary angiogram.[25] They found that the neutrophil to lymphocyte ratio was significantly higher in patients in both ectasia and CAD groups compared to those in the normal coronary group. Our finding is in line with the previous studies, and the larger population of our study has provided a greater power for the study.

Contrary to our findings, one study showed that patients with isolated CAE had a significantly higher neutrophil to lymphocyte ratio than patients with obstructive CAD and control groups.[26] These authors concluded that a more severe inflammatory process could be involved in the development of CAE. We also observed a slightly higher level of neutrophil to lymphocyte ratio in the coronary ectasia group albeit the difference with the CAD group was not statistically significant.

Many other blood-related markers such as mean platelet volume and red cell distribution wide have been shown to be associated with the presence of CAE[25,27] although their exact relationship demands further investigations.

Study limitations

Our study has also some limitations. First, we did not measure other inflammatory markers such as CRP and did not compare it to neutrophil to lymphocyte ratio. Furthermore, this was a single-center study and our center is a tertiary referral hospital, so patients who are referred to our center may have different characteristics than the general population.

Conclusion

Higher neutrophil to lymphocyte ratio was present in patients with CAE and CAD patients than the normal coronary individuals. This suggests an inflammatory basis for the pathogenesis of coronary ectasia. Further studies are required to understand the exact mechanism behind this inflammatory process and discriminate the pathogenesis of ectasia from atherosclerosis.

Acknowledgment

This study was part of the thesis by Dr. Seyed Ali Mousavi for obtaining a specialty degree in Cardiology. This work was supported by Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran. The authors sincerely thank the staff of the Catheterization laboratory of Tehran Heart Center and Dr. Seyed Hasan Molana for the language edit of this article.

Financial support and sponsorship

This study was financially supported by Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.

Conflicts of interest

There are no conflicts of interest.

References

1. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients. Br Heart J 1985;54:392-5.
2. Syed M, Lesch M. Coronary artery aneurysm: A review. Prog Cardiovasc Dis 1997;40:77-84.
3. Ozcan OU, Gulec S. Coronary artery ectasia. Cor vasa 2013;55:e242-e7.
4. Mavrogeni S. Coronary artery ectasia: From diagnosis to treatment. Hellenic J Cardiol 2010;51:158-63.
5. Díaz-Zamudio M, Bacilio-Pérez U, Herrera-Zarza MC, Meave-González A, Alexanderson-Rosas E, Zambrana-Balta GF, *et al.* Coronary artery aneurysms and ectasia: Role of coronary CT angiography. Radiographics 2009;29:1939-54.
6. Song R, Liu G, Li X, Xu W, Liu J, Jin H, *et al.* Elevated inducible nitric oxide levels and decreased hydrogen sulfide levels can predict the risk of coronary artery ectasia in kawasaki disease. Pediatr Cardiol 2016;37:322-9.
7. Farrag A, Faramawy AE, Salem MA, Wahab RA, Ghareeb S. Coronary artery ectasia diagnosed using multidetector computed tomography: Morphology and relation to coronary artery calcification. Int J Cardiovasc Imaging 2013;29:427-33.
8. Fariba F, Moradi M, Arabi A, Ghaderi B. Prevalence of coronary artery ectasia with atherosclerosis and associated risk factors in the west of iran: A Cross-sectional study. J Res Health Sci 2016;16:22-5.
9. Triantafyllis AS, Kalogeropoulos AS, Rigopoulos AG, Sakadakis EA, Toumpoulis IK, Tsikrikas S, *et al.* Coronary artery ectasia and inflammatory cytokines: Link with a predominant Th-2 immune response? Cytokine 2013;64:427-32.
10. Brunetti ND, Salvemini G, Cuculo A, Ruggiero A, De Gennaro L, Gaglione A, *et al.* Coronary artery ectasia is related to coronary slow flow and inflammatory activation. Atherosclerosis 2014;233:636-40.
11. Erayman A, Sen N. Neutrophil–lymphocyte ratio and C-reactive protein may be correlated in patients with coronary artery ectasia. Angiology 2014;65:84-5.
12. Ammar W, Kappary M, Baghdady Y, Shehata M. Matrix metalloproteinase-9 (MMP9) and high sensitivity C-reactive protein (hs-CRP) in coronary artery ectasia (CAE). Eur Heart J 2013;34:P5501.
13. Dogan A, Arslan A, Yucel H, Aksoy F, Icli A, Ozaydin M, *et al.* Gamma glutamyltransferase, inflammation and cardiovascular risk factors in isolated coronary artery ectasia. Rev Port Cardiol 2016;35:33-9.
14. Savino M, Parisi Q, Biondi-Zoccai GG, Pristipino C, Cianflone D, Crea F, *et al.* New insights into molecular mechanisms of diffuse coronary ectasiae: A possible role for VEGF. Int J Cardiol 2006;106:307-12.
15. Kaya H, Ertaş F, İslamoğlu Y, Kaya Z, Atılgan ZA, Çil H, *et al.* Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost 2014;20:50-4.
16. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, *et al.* Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010;105:186-91.
17. Turhan H, Erbay AR, Yasar AS, Aksoy Y, Bicer A, Yetkin G, *et al.* Plasma soluble adhesion molecules; intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin levels in patients with isolated coronary artery ectasia. Coron Artery Dis 2005;16:45-50.
18. Yilmaz H, Tayyareci G, Sayar N, Gurkan U, Tangurek B, Asilturk R, *et al.* Plasma soluble adhesion molecule levels in coronary artery ectasia. Cardiology 2006;105:176-81.
19. Turhan H, Erbay AR, Yasar AS, Balci M, Bicer A, Yetkin E, *et al.* Comparison of C-reactive protein levels in patients with coronary artery ectasia versus patients with obstructive coronary artery disease. Am J Cardiol 2004;94:1303-6.
20. Finkelstein A, Michowitz Y, Abashidze A, Miller H, Keren G, George J, *et al.* Temporal association between circulating proteolytic, inflammatory and neurohormonal markers in patients with coronary ectasia. Atherosclerosis 2005;179:353-9.
21. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, *et al.* Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012;225:456-60.
22. Açar G, Fidan S, Uslu ZA, Turkday S, Avci A, Alizade E, *et al.* Relationship of neutrophil-lymphocyte ratio with the presence, severity, and extent of coronary atherosclerosis detected by coronary computed tomography angiography. Angiology 2015;66:174-9.
23. Ayhan SS, Oztürk S, Erdem A, Ozlü MF, Ozyaşar M, Erdem K, *et al.* Relation of neutrophil/lymphocyte ratio with the presence and severity of coronary artery ectasia. Turk Kardiyol Dern Ars 2013;41:185-90.
24. Işık T, Ayhan E, Uyarel H, Tanboğa IH, Kurt M, Uluganyan M, *et al.* Association of neutrophil to lymphocyte ratio with presence of isolated coronary artery ectasia. Turk Kardiyol Dern Ars 2013;41:123-30.
25. Balta S, Demirkol S, Celik T, Kucuk U, Unlu M, Arslan Z, *et al.* Association between coronary artery ectasia and neutrophil-lymphocyte ratio. Angiology 2013;64:627-32.
26. Kalaycıoğlu E, Gökdeniz T, Aykan AC, Gül I, Boyacı F, Gürsoy OM, *et al.* Comparison of neutrophil to lymphocyte ratio in patients with coronary artery ectasia versus patients with obstructive coronary artery disease. Kardiol Pol 2014;72:372-80.
27. Dogdu O, Koc F, Kalay N, Yarlioglues M, Elcik D, Karayakali M, *et al.* Assessment of red cell distribution width (RDW) in patients with coronary artery ectasia. Clin Appl Thromb Hemost 2012;18:211-4.