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Relationship between leucocytosis and left ventricular ejection fraction in patients with acute myocardial infarction

Rahime Eskandarian[1], MD, *Raheb Ghorbani*[2], PhD, *Zahra Asgary*[3], MD

INTRODUCTION Myocardial infarction (MI) is common and affects a significant number of people annually. Death occurs due to either arrhythmia or heart failure. As leucocytosis, especially elevated neutrophil count, is a hallmark of inflammatory reactions in patients with MI, we investigated the relationship between leucocytosis on admission and left ventricular ejection fraction (LVEF) in patients with acute MI (AMI).

METHODS Patients with AMI were enrolled in a case-control study. Blood samples obtained in the first 24 hours after the onset of pain were analysed for cardiac enzyme levels and cell count. Echocardiography was performed on Days 3–5. Patients with LVEF < 45% were assigned to the left ventricular (LV) systolic dysfunction group (n = 69) and those with LVEF ≥ 45% were taken as controls (n = 69). All patients were matched for variables such as hypertension, diabetes mellitus, hyperlipidaemia, family history of cardiac disease, age and gender.

RESULTS Leucocytosis was higher in patients with systolic dysfunction (47.8%) when compared with the controls (20.3%), and was significantly associated with the development of LV systolic dysfunction (p = 0.001). Similarly, neutrophilia was more common in patients with systolic dysfunction than the controls (6.6% vs. 34.8%), and was significantly associated with LV systolic dysfunction (p < 0.001). Monocytosis was higher in the controls than the systolic dysfunction group (40.6% vs. 33.3%; p = 0.378).

CONCLUSION Leucocytosis and neutrophilia in the acute phase of MI are important predictive factors for the development of LV systolic dysfunction. Leucocytosis can be used for risk stratification of such patients.

Keywords: acute myocardial infarction, left ventricular systolic dysfunction, leucocytosis, monocytosis, neutrophilia
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INTRODUCTION

Myocardial infarction (MI) is common and affects a significant proportion of the population each year. Death in these patients is due to either arrhythmia or heart failure.[1] Left ventricular (LV) systolic dysfunction is a prevalent complication following MI, and it is associated with a high mortality rate.[2] In these patients, the incidence of reinfarction is considerable.[3] The post-infarction inflammatory process and alterations in the involved area cause a change in the morphology, size and thickness of the infarct and non-infarct areas, and it is these processes and the associated changes that are a harbinger of LV systolic dysfunction, known as remodelling.[1] The determination of LV function using echocardiography is therefore valuable in predicting the prognosis and comparable to angiographic studies.[1,4]

The nonspecific reaction to MI is accompanied by an elevation of blood leucocytes, especially neutrophils that are increased in the first few hours of infarction and return to normal within a week. It is not yet known whether such leucocytosis can contribute to myocardial damage.[1,4] However, leucocytes, especially neutrophils, are an indicator of the intensity of the inflammatory reaction. Some authors have observed that leucocytosis on hospital admission is related to subsequent LV systolic dysfunction and heart failure, while others have suggested that leucocytosis is a predictive factor for heart failure.[5-10] As leucocytosis was found to be linked in some studies to the progression of MI, deterioration of complications and increased mortality, white blood cells (WBCs) and neutrophils have been suggested to be an independent factor of prognosis in patients with MI.[5] As neutrophils can partly cause vascular damage, their count may also reflect the severity of this process.[1]

The authors found a paucity of literature based on studies that completely and simultaneously investigated all the factors reported to be associated with MI in a design matched for risk factors, age and gender. In view of the abovementioned observations and the probable relationship between leucocytosis, neutrophilia and monocytosis on admission in patients with MI and the major complications seen in them (such as LV systolic dysfunction), this study was designed so that prompt and aggressive measures could be taken to treat such patients in case a relationship was established.

METHODS

A case-control study was conducted at Fatemieh Hospital, Semnan, Iran, on patients with acute MI (AMI) from March 2006 to September 2006. Written consent was obtained from all patients. Blood samples were obtained at the time of admission, within 6–24 hours of the onset of chest pain, and sent for cardiac enzyme assessments and blood cell count. WBC counts were measured

[1]Department of Interventional Cardiology, [2]Department of Biostatistics, [3]Fatemieh Hospital, Semnan University of Medical Sciences, Semnan, Iran
Correspondence: Dr Rahime Eskandarian, Assistant Professor, Department of Interventional Cardiology, Fatemieh Hospital, 17th Shahrivar Boulevard, Semnan 3517894431, Iran. rheskandarian@yahoo.com

using standard techniques and expressed as absolute count/mm^3. Total WBC was counted in ethylenediaminetetraacetic acid-anticoagulated whole blood specimens using the Sysmex XE 2100 automated haematology analyser (Sysmex Corporation, Kobe, Japan). Echocardiography was performed for patients on Days 3–5 of hospital stay. 69 patients with left ventricular ejection fraction (LVEF) < 45% were assigned to the LV systolic dysfunction group (test group), while 69 patients who had LVEF ≥ 45% were assigned to the control group. The controls were matched for variables such as hypertension, diabetes mellitus, hyperlipidaemia, family history of cardiac disease, age and gender.

The diagnosis of acute ST segment elevation MI was based on the presence of chest pain lasting ≥ 30 minutes and associated with typical changes on surface electrocardiogram (ST segment elevation ≥ 0.1 mV in two or more limb leads or ≥ 0.2 mV in two or more contiguous precordial leads, pathological Q waves, or complete left bundle branch block of new onset) with elevated cardiac enzymes such as elevated troponin T (troponin T level > 0.03 µg/L), creatine kinase or creatine kinase-myocardial band (CK-MB). Arterial hypertension was defined in the presence of active treatment with antihypertensive medications or documentation of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two separate occasions. Hypercholesterolaemia was defined as documented total cholesterol ≥ 240 mg/dL. Current smokers were defined as those currently smoking tobacco. Diabetes mellitus was defined as patients under active treatment with insulin or oral hypoglycaemic agents. Leucocytosis was defined as leucocyte count > 11,000/mm^3, and monocytosis and neutrophilia as monocyte > 2% and neutrophil > 65%, respectively.[11]

Exclusion criteria included: (a) treatment with steroids, nonsteroidal anti-inflammatory drugs or antibiotics in the preceding week; (b) acute infection (such as urinary, respiratory, gastrointestinal and oral cavity infection) in the preceding two weeks; (c) surgery in the preceding two weeks; (d) malignancy; (e) liver and renal failure; (f) patients with febrile disorders, or acute or chronic inflammatory disease, vacuities or gastrointestinal bleeding in the preceding month; (g) hospital admission later than 24 hours after the onset of MI symptoms; (h) laboratory tests later than 24 hours after the onset of pain or without an echocardiography report; and (i) history of MI or heart failure.

The study was approved by the hospital's ethics committee. Data were analysed using the Statistical Package for the Social Sciences for Windows version 13.0 (SPSS Inc, Chicago, IL, USA). Comparisons between the test and control groups were made using the *t*-test for continuous variables and the chi-square test for discrete variables. All baseline, demographic and clinical variables were entered into the model. A p-value < 0.05 was considered statistically significant.

RESULTS

138 patients, with and without LV systolic dysfunction, were divided into two groups of 69 patients each. The average age of the patients was 62.5 ± 12.9 years in the test group and 61.8 ± 13.6 years in the control group (p = 0.783). 18.8% of patients with LV systolic dysfunction were men and 82.6% of the controls were women. The gender distribution was homogenous between the two patient groups (p = 0.859). Patients from the test and control groups were compared with regard to major cardiac risk factors such as diabetes mellitus (20.3% vs. 23.2%; p = 0.680), hypertension (29% vs. 27.9%; p = 0.892), smoking (26.1% vs. 29%; p = 0.703), hyperlipidaemia (17.4% vs. 20.3%; p = 0.666) and family history of cardiac disease (5.8% vs. 4.3%; p = 0.466) [Table I].

Table I. Characteristics of patients.

Characteristic	No. (%)		p-value
	Test group (n = 69)	Control group (n = 69)	
Age (years)			0.783
< 60	32 (46.4)	34 (49.3)	
≥ 60	37 (53.6)	35 (50.7)	
Gender			0.859
Men	13 (18.8)	12 (17.4)	
Women	56 (81.2)	57 (82.6)	
Diabetes mellitus			0.680
Yes	14 (20.3)	16 (23.2)	
No	55 (79.7)	53 (76.8)	
Hypertension			0.892
Yes	20 (29)	19 (27.9)	
No	49 (71)	50 (72.1)	
Hyperlipidaemia			0.666
Yes	14 (17.4)	12 (20.3)	
No	55 (82.6)	57 (79.7)	
Smoking			0.703
Yes	18 (26.1)	20 (29)	
No	51 (73.9)	49 (71)	
Family history of cardiac disease			0.466
Yes	4 (5.8)	3 (4.3)	
No	65 (94.2)	66 (95.7)	

Leucocytosis was observed in 47.8% of patients with systolic dysfunction when compared to the controls (20.3%), and a significant association was found between leucocytosis and the development of heart failure (p = 0.001; odds ratio [OR] 3.60, 95% confidence interval [CI] 1.98–9.35). Similarly, neutrophilia was more common among patients with systolic dysfunction (69.6%) than among the controls (34.8%), with neutrophilia and LV systolic dysfunction showing a significant association (p < 0.001; OR 4.29, 95% CI 1.98–9.35). However, only 33.3% of test patients had monocytosis (monocyte > 2%) compared to 40.6% of the controls. The association between monocytosis and LV systolic dysfunction was not significant (p = 0.378; OR 0.73, 95% CI 0.34–1.55, Table II).

DISCUSSION

Recent studies have shown that inflammation plays a major role in atherosclerosis and acute coronary syndrome.[12] Sabatine et al found that leucocytes caused altered stress-induced adhesion (such as stress ischaemia, and acute and chronic endothelial damage) and bonding with toxic oxygen moieties or proteolytic

Table II. Relationship of leucocytosis, neutrophilia and monocytosis with heart failure in patients with acute myocardial infarction.

Characteristic	No. (%)		p-value
	Test group (n = 69)	Control group (n = 69)	
Leucocytosis			0.001
Yes	33 (47.8)	14 (20.3)	
No	36 (52.2)	55 (79.7)	
Neutrophilia			< 0.001
Yes	48 (69.6)	24 (34.8)	
No	21 (30.4)	45 (65.2)	
Monocytosis			0.378
Yes	23 (33.3)	28 (40.6)	
No	46 (66.7)	41 (59.4)	

enzymes.[13] According to Murtagh and Anderson, neutrophils, monocytes and special tissue macrophages (such as those in an atherosclerotic plaque) secrete myoperoxidase, an enzyme that is secreted through the activation and degranulation of leucocytes.[14] Myoperoxidase changes low-density lipoprotein so that it is more rapidly absorbed by macrophages, increases foam cell production and decreases nitric oxide. According to these authors, high levels of myoperoxidase in leucocytes and circulation is an important prognostic factor in cardiac patients.[14]

The association between leucocyte count and cardiac disease has been known for years. Elevated leucocyte counts can increase cardiac disease, cardiac events in unstable angina and patients with MI, and are associated with increased mortality.[15-17] Several studies have investigated the relationship between leucocytosis and heart failure, or its effect on the short- and long-term prognosis in patients with MI.[18-20] According to Grzybowski et al, leucocytosis is associated with complications such as cardiac failure, cardiogenic shock and in-hospital death, and is an important predictive factor for intrahospital complications.[5] Various studies have also reported that leucocytosis is an independent factor for reinfarction, and intrahospital and one-month mortalities.[3,14,21-24]

As leucocyte assessments are cheap and routinely performed, some authors have suggested that these should be used for risk stratification of such patients.[5,21] Antman and Braunwald, as well as Green et al, have proposed that leucocyte elevation is a sensitive test for the diagnosis of MI, as it is associated with impaired perfusion in the epicardium and myocardium.[4,10] This was supported by Hansen's study, which found that an elevated WBC count was accompanied by decreased epicardial and myocardial perfusion, thromboresistance (delayed patency of the artery and more thrombus formation) and a higher likelihood of cardiac failure and death.[23]

Elevated leucocyte counts have been shown to be associated with resistance to thrombolysis and vessel patency 60 minutes and 90 minutes after the administration of thrombolytics, as well as increased thrombus formation following patency in patients with acute MI.[25] Defective microvascularity has also been noted in association with leucocytosis.[26] A possible explanation for this could be that, following MI, leucocytes generated from tissue necrosis are less flexible and fail to completely cross the microcirculation. This may worsen ischaemia and enlarge the infarct area, as leucocytes are larger and stiffer than red blood cells and platelets, and can therefore occlude small arteries.[27]

According to Mueller et al, hypercoagulability, endothelial dysfunction, necrosis of proinflammatory myocytes and a 'no-reflow' phenomenon are all associated with leucocytosis.[21] Additionally, during reperfusion of the ischaemic tissue, neutrophils and platelets form plaques in the microvasculature and cause no-reflow, ventricular arrhythmia, loss of vascular reserve, enlargement of the infarct area, and eventually, decreased ventricular function.[28-30] We found that leucocytosis was more common in patients with systolic dysfunction than the controls, and was significantly associated with the development of heart failure. Likewise, neutrophilia was also higher among patients with systolic dysfunction than among those without such dysfunction, and was also significantly associated with the development of heart failure. While monocytosis was higher in the controls than in patients with systolic dysfunction, the association between monocytosis and LV systolic dysfunction was not significant in our series. Our findings indicate that in the acute phase of MI, leucocytosis and neutrophilia are important predictive factors for heart failure – patients with leucocytosis were 3.60 times more likely to develop heart failure, while those with neutrophilia had a 4.29 times higher risk of developing heart failure.

In summary, leucocytosis is a nonspecific indicator of inflammation in patients with MI and should be regarded as an important predictive factor for the development of LV systolic dysfunction. Leucocytosis can be used for risk stratification of such patients.

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