Relationship between Monocytosis and Congestive Heart Failure after Acute Myocardial Infarction

Abdullah Amirfarhangi, MD and Samad Ghaffari, MD

Abstract

Objectives- The aim of this study was to determine the significance of peripheral monocytosis in the early progression to congestive heart failure (CHF).

Background- Peripheral leukocytosis and monocytosis occur after AMI, especially at the 3rd day, reflecting infiltration of monocytes and macrophages into the necrotic myocardium. The relationship between peak 3rd day monocytosis with the progression to AMI complications was established earlier. However, the prognostic significance of the 1st day monocytosis after AMI remains to be determined.

Methods- From a total of 165 patients with first Q-wave AMI, studied after admission from 2002 to 2003, 101 patients were selected. The CBC H1 test at the first 24 hrs, echocardiographic study and physical exam in the first 4 days of the onset of AMI were evaluated. The association between peripheral monocytosis and progression to CHF after AMI was assessed.

Results- Of all the patients (101cases), 40 (39.4 percent) patients had monocytosis equal or more than 620. Forty-seven (46.5 percent) patients were CHF-positive. The patients with CHF had 13085±4095/mm total WBC count, whereas the others had 10428±3256/mm ($p<0.001$). PMN count in the CHF and normal groups was 10927±4205/mm and 8299±3137/mm, respectively ($p<0.01$). The mean of monocyte count in the CHF-positive group was 740.8±334/mm in comparison with that in the CHF-negative group, 516±26/mm ($p=0.0001$). The mean of the EF in the CHF-positive patients was 33.8±10.3 percent versus the 40.7±7.7 percent in the CHF-negative patients ($P=0.0001$).

Conclusion- Peripheral monocytosis in the first 24 hrs after AMI is associated with CHF, suggesting a possible role of monocytosis as the bedside marker of CHF evolution in the hospitalization period. Clinical markers that can predict which patients are prone to develop adverse LV structural remodeling and post-MI complications, therefore, would be very useful in the prevention of them ***(Iranian Heart Journal 2004; 5(3):34-39).***

Key words: monocytosis■ congestive heart failure ■ acute myocardial infarction ■ complications

Over the last decade, there has been growing interest in bedside protein and cellular markers of inflammation and adverse outcome after acute myocardial infarction (AMI).[1-12] Clinical studies have demonstrated the presence of activated circulating neutrophils; lymphocytes and monocytes; increased levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1); IL-6; tumor necrosis factor alpha (TNF-alpha); and acute–phase reactants, such as C-reactive protein (CRP).[10] Several studies have documented leukocytosis after AMI.[2,7,11] In the Worcester heart attack study[2], an elevated white blood cell (WBC) count correlated

Correspondence to: A. Amir Farhangi MD, Dept. of Cardiology, Shaheed Rajaei Cardiovascular Medical Center, Tehran, Iran
From the Dept. of Cardiology, Madani Heart Hospital, Tabriz, Iran. Tel: 0098 21-23922844 Email: amirfarhangi@hotmail.com

with in-hospital mortality and recurrent infarction. In the Study of Left Ventricular Dysfunction (SOLVD),[8] a retrospective analysis revealed that the baseline WBC count was an independent predictor of mortality in patients with LV dysfunction. The WBC count after AMI was proposed for risk stratification of patients.[11] An elevated neutrophil count was reported to correlate with pump failure after AMI.[9] The pro-coagulant activity of peripheral monocytes and polymorphonuclear neutrophils after AMI was suggested to exacerbate the disease process.[6]

The cellular response after AMI and reperfusion has been reviewed.[2,7,14,17] Following AMI, neutrophils appear very early after reperfusion.[7] Monocytes then migrate along the endothelial wall, interact with adhesion molecules and move into infarct zone, where they transform into macrophages, which become activated.[13] Macrophages and monocytes outnumber neutrophils by two to three days.[4,18] The macrophages and monocytes secrete factors increasing monocytopoiesis, IL-6, macrophage colony stimulating factor (M-CSF) and monocyte chemoattractant protein-1 (MCP-1).[14,16] These monocyte related cytokines lead to peripheral monocytosis and monocyte infiltration of the infarct zone, suggesting that acute monocyte recruitment may be involved in infarct healing. Macrophages also secrete cytokines that stimulate fibroblast proliferation and collagen deposition, which are important during infarct healing. The monocyte-related cytokines (such as IL-1, IL-6 and TNF-alpha) stimulate liver cells to produce CRP. A correlation between IL-6 and serum CRP has been demonstrated in patients with AMI.[15] Meisel et al.[4] found a correlation between peripheral monocytosis and peak creatinine kinase (CK) as an index of infarct size. In a study of patients with a first Q-wave AMI, Anzai et al.[3] found an association between CRP and infarct expansion, subacute cardiac rupture, LV aneurysm and adverse long-term outcome. Recently, Maekawa et al.[13] reported that the peak 3rd day monocytosis after AMI correlated positively with LV end-diastolic volume and negatively with ejection fraction on the pre-discharge left ventriculograms. They found that the elevated monocyte count was an independent determinant of pump failure, LV aneurysms and cardiac events, such as readmission for heart failure, recurrent infarction, cardiac death and sudden death.

In this study, we focused on the prognostic significance of hospital arrival time monocytosis with the early progression to heart failure in the patients with first Q-wave myocardial infarction.

Methods

Study population

We examined 165 consecutive patients with first Q-wave AMI admitted to Shahid Madani Heart Center of Tabriz University within 24h after the onset of symptoms from 2002 to 2003. A diagnosis of Q-wave AMI was made on a combination of chest pain, elevated enzymes and electrocardiographic findings. We excluded patients in whom the time elapsed from the onset of chest pain to admission was greater than 24hr and those who died or were in heart failure at the time of admission. Also, patients with previous trauma in the past week, any malignancy in the past 3 years, any infection in the past week except for common cold, corticosteroid consumption, history of surgical procedure in the last week and previously diagnosed heart failure were excluded. Finally, 101 patients were included in this study.

Study protocol

The following data were obtained: age; gender; previous coronary syndromes; time of pain onset; information about exclusive

criteria; presence of risk factors, such as hypertension, diabetes mellitus and smoking; their duration and type of medication before and after admission, such as aspirin, beta blocker agents, diuretics, ACE inhibitors and digoxin; and in-hospital complications. As mentioned above, the patients who died in hospital or had a grade of class 2 or greater according to the Killips classification were excluded from the study. The blood samples were taken, and total and differential count of leukocytes was measured by an automated hematology analyzer (CBC H1 system) on admission. Serum samples were analyzed for creatinine kinase level. The site of infarction was determined, and history of PTCA vs. thrombolytic therapy was recorded. On the 3rd or 4th day of admission, all the patients underwent echocardiographic examination for ejection fraction determination. At this time, we looked for the signs and symptoms of heart failure according to the Framingham criteria.

Statistical analysis

Continuous data are expressed as the mean value ± SD. For continuous variables, cases in the 3rd SD from mean were excluded from the analysis. A comparison was made between the groups using the unpaired *t*-test and non-parametric tests. For nominal and categorical variables, Chi-square test was applied. Multiple logistic regression analysis was used to assess the effect of various factors on pump failure. To determine the cut-off point of monocytes to predict the evaluation of heart failure, receiver operating characteristic (ROC) analysis was performed. A p value <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS 11.5 software.

Results

Demographic data

The mean age of all the patients was 59.8±11years (ranging from 37 to 84 years). The mean interval from the onset of pain to arrival at hospital was 5.8±4.3 hours. Eighty-seven (86%) cases were male and 14 (14%) were female. Forty-two patients (41.5%) had a history of CAD, 54 patients (53.4%) were smokers, 16 patients (15.8%) were diabetic and 35 patients (34.5%) were hypertensive. The mean WBC count on admission was 11665±3887/mm, and the monocyte count was 621±317/mm. The mean value of CPK was 1840±1040, and CK-MB isoenzyme was 225±203. The prevalent site of MI was the inferior wall (29.7%), followed by the anteroseptal (18.8%) and anterior walls (14.9%).

Sixty-eight patients received thrombolytics as a revascularization therapy; none of them had PTCA. The monocyte count did not significantly differ according to patients' characteristics (Table I).

Table I. Patients' characteristics according to monocytic groups.

	monocyte> 620 (n=61)	monocyte< 620 (n=40)	P value
Age	61.5+10.1	57.3+12.1	0.063
Gender(male)	52 (85.2 %)	35 (87.5%)	0.748
CAD	25 (40.9 %)	17 (42.5 %)	0.880
HTN	20 (32.7 %)	15 (37.5 %)	0.625
DM	13 (21.3 %)	3 (7.5 %)	0.063
smoking	29 (47.5 %)	25 (62.5 %)	0.140
aspirin	61 (100 %)	40 (100%)	-
digoxin	3 (4.9 %)	0 (0 %)	0.154
diuretic	8 (13.1 %)	11 (27.5 %)	0.070
nitrate	49 (80.3 %)	32 (80 %)	0.968
Beta blocker	50 (81.9 %)	29 (72.5 %)	0.260
ACEI	53 (86.8 %)	35 (87.5 %)	0.928
Calcium CB	10 (16.3 %)	6 (15 %)	0.851
heparin	55 (90.1 %)	34 (85 %)	0.433
CPK	1674+964	2091+1112	0.048 *
CKMB	212+197	246+212	0.416
EF<30%	8 (13%)	7 (18%)	0.03*
Total WBC	10446+3199	13523+4139	0.0001 **
PMN	8633+3319	10897+4314	0.004 **
CHF	20(33%)	27(75%)	0.0001**

*Significant at the 0.05 level
**Significant at the 0.01 level

Relation between heart failure and monocyte count

Of the 101 patients, 47 (46.5%) met the Framingham criteria of heart failure in the first four days of admission (Table II).

There is a strongly-positive relation between the total WBC and polymorpho-nuclear count and the evolution of heart failure. While the mean WBC count in the CHF group was 13085±4095/mm, it was 10428±3256/mm (P<0.001) in the control group. The mean PMN was also significantly different in both groups (10927±4205 vs. 8299±3137; p<0.01). The heart failure group had 740.8±334/mm monocytes in comparison with 516±262/mm for the normal patients (p<0.001). The cut-off point of monocytosis was 620/mm. In the group with <620/mm monocytes, 8 (13%) patients had EF<30%, whereas 7 (18%) patients had EF<30% (p<0.03) in the other group with monocytes >620/mm.

Table II. Patients' characteristics according to CHF groups.

	CHF (+) N=47	CHF (-) N=54	P value
age	60.9+10.7	58.9+11.4	0.359
gender(male)	41 (87 %)	46 (85.1 %)	0.766
CAD	19 (40.4 %)	23 (42.5 %)	0.826
HTN	17 (36.1 %)	18 (33.3 %)	0.756
DM	6 (12.7 %)	10 (18.5 %)	0.430
smoking	25 (53.1 %)	29 (53.7 %)	0.959
aspirin	47 (100 %)	54 (100 %)	-
digoxin	2 (4.2 %)	1 (1.8 %)	0.478
duretic	15 (31.9 %)	4 (7.4 %)	0.002**
nitrate	35 (74.4 %)	46 (85.1 %)	0.178
blocker beta	31 (65.9 %)	48 (88.8 %)	0.005**
CB calcium	11 (23.4 %)	5 (9.2 %)	0.052
heparin	39 (82.9 %)	50 (92.5 %)	0.136
Total WBC	13085+4095	10428+3256	0.0001**
PMN	10927+4205	8299+3137	0.001**
MONO	740.8+334	516+262	0.0001**
MonoGroup <620	27 (57.4 %)	13 (24 %)	0.001**
EF	33.8+10.3	40.7+7.7	0.0001**
EF< 40 %	29 (61.7 %)	17 (31.4 %)	0.002**
CPK	2018+1120	1684+949	0.109
CK-MB	271+244	186+150	0.03*
fibrinolytic	30 (63.8 %)	38 (70.3 %)	0.485

*Significant at the 0.05 level
**Significant at the 0.01 level

The CPK level was not significantly different in both CHF and normal groups (2018±1120 vs. 1684±949; p=0.109), but the mean value of CK-MB level differed significantly between the groups (271±244 vs. 186±150; p<0.03). The evolution of early CHF was not related to the fibrinolytic therapy in this study (p=0.485) in spite of the lesser use of it in the CHF group (63% vs. 70%).

Relation of CHF with other variables

There is no relation between age, gender, history of CAD and progression to early heart failure after AMI. Despite the basic role of hypertension, diabetes mellitus and smoking in the formation of atherosclerosis and AMI, these risk factors were not statistically related to heart failure.

Discussion

Our findings showed that monocytosis on admission had a significant positive correlation with early progression to CHF during the first four days after AMI. Patients with heart failure had higher monocyte counts than those without heart failure. Multivariate analysis suggested that monocytosis >620/mm was an independent factor for the determination of heart failure after AMI.

A relation between leukocytosis and the prognosis of patients with AMI has been demonstrated previously.[2,811,12] Some investigators reported that a higher neutrophil percentage count >65% on admission time was an independent predictor of pump failure after AMI.[9] Meisel et al.[4] established that peripheral monocytosis in the first three days after AMI as an indicator of post-MI inflammation could predict the outcome of disease. Finally Maekawa et al. addressed the prognostic significance of peripheral monocytosis, found at two to three days after reperfused AMI, as a cellular marker

for clinical outcome and its possible role in left ventricular remodeling.[19]

In this study, we showed that on-admission neutrophilia and monocytosis could predict the evolution of heart failure in the early phase of admission. Monocytosis at two to three days after injury can be answered with the local infiltration of neutrophils, followed by monocytes in the infarcted site. The magnitude of infarct size can predict the severity of monocytosis. The greater the magnitude of monocytosis is, the larger the infarction tends to be. However, there is no direct evidence in the present study to show that the increased peripheral monocytes infiltration into the necrotic myocardium contributes to the infarct healing process. Moreover, previous pathologic studies indicate that peripheral monocytosis precedes an increase in the number of monocytes and macrophages in the infarcted tissue.[19] In this study, we looked for the relation between early monocytosis before the completion of infarcted site inflammation processes and the disease outcome. In other words, this monocytosis is apart from the migration of monocytes to the infarcted zone. Whether this phenomenon is an indicator of pre-infarction inflammation states such as CRP, which is related to the instability of plaques and infarction size, or it is a concomitant process with infarction such as PMNs or a very rapidly inflammatory response are questions that require further investigation.

Conclusion

This study demonstrated that peripheral monocytosis is associated with early progression to pump failure. Further detailed studies are needed to determine whether this finding would be confirmed in larger clinical trials.

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