Immunological changes in acute myocardial infarction

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ABSTRACT

Objective: This study was undertaken to investigate troponin and lymphocyte subset changes in acute myocardial infarctions (AMI) and to correlate these changes with disease variables.

Methods: Forty-five patients with AMI admitted to the Coronary Care Unit, Jordan University Hospital and Queen Alia Heart Institute at King Hussein Medical Center, Amman, Jordan during the period November 1999 through to April 2000 were included in the study. Forty-five patients with non cardiac conditions were selected as a control group. Tests performed include; determination of the percentages of B-lymphocytes, T-lymphocytes and T-lymphocyte subsets by flow cytometry, measurements of serum cardiac troponin I (cTnI) by microparticle enzyme immunoassay and determination of minor blood groups by the gel test.

Results: A significant increase in the percentages of $CD8^+$ and $CD19^+$ cells combined with a significant decrease in the percentages of $CD3^+$ and $CD4^+$ cells as well as a decrease of $CD4^+/CD8^+$ ratio were documented in patients with AMI 24 hours after admission to the hospital. Except for $CD19^+$ cells, all of cell types assayed for returned to their normal percentages before discharge of patients. Very low $CD4^+$ cell percentages and $CD4^+/CD8^+$ ratio were found to be poor prognostic signs of AMI. Serum cTnI levels which were elevated in all patients correlate very well with the decreased $CD4^+$ cell percentages, and the decreased $CD4^+/CD8^+$ cell ratio and they seem to correlate with the extensiveness of infarction. Troponin and lymphocyte subset changes, on the other hand, did not correlate with the number of vessels diseased or the risk factors for AMI. Finally, a statistically significant association was observed between the Le (a^-b^-) phenotype and AMI.

Conclusion: Immunologic change seem to accompany or follow AMI and changes in T-lymphocyte subsets and cTnI can be regarded as prognostic markers in AMI but these changes are independent of risk factors and the number of vessels diseased.

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Acute myocardial infarction (AMI) is a very common cause of death worldwide.[1] Specific immunological mechanisms were shown to be involved in atherogenesis and the consequent development of ischemic heart disease (IHD).[2,3] Immunological changes have not been, however, fully characterized in AMI as a few reports were published in this regard and they were occasionally controversial.[4-12] A significant decrease in $CD4^+$ T cells percentage with a decreased or inverted $CD4^+/CD8^+$ T cell ratio were reported to take place early after the onset of AMI.[4,5,7] Tsuchihashi et al,[10] on the other hand, reported that $CD4^+$ cell percentage was significantly higher and $CD8^+$ cell percentage was significantly lower in patients with AMI. Significantly diminished delayed type hypersensitivity and reduced T cell counts were documented in patients with AMI, particularly those who died of it.[13] Likewise, Van Offel et al[14] found that patients who died of AMI had impaired in vivo and in vitro immune responses. To the contrary, Tsuchihashi et al[10] claimed that the immunological

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competence was enhanced in patients with AMI and that there was no significant correlation between infarct size and changes in lymphocyte subsets. Cardiac troponin I (cTnI) has been regarded as the best marker for the definitive diagnosis of AMI and that its levels correlated well with the myocardial infarct size[15-17] although it is not recommended for infarct sizing. The association between minor blood groups and AMI has been investigated, and findings were largely controversial.[18,19] The Le (a^-b^-) phenotype was reported by many authors to be a risk factor in the development of IHD in general and AMI in particular.[18-22] The aim of this study was to investigate changes that take place in lymphocyte subpopulations and cardiac troponin and to correlate these changes with risk factors and disease variables.

Methods. ***Study population.*** Forty-five patients with AMI were included in this study, thirty-nine of whom had Q-wave AMI and 6 had non Q-wave AMI. They were admitted to the Coronary Care Units (CCU) of 2 major hospitals in Amman, Jordan. The Jordan University Hospital and Queen Alia Heart Institute, during the period between November 1999 and April 2000. Of the patients, 34 were males, 11 were females, and they ranged in age from 40-73-years. Each patient was matched with one randomly selected control that met the matching criteria of age ±1 year; sex and who did not have any history of IHD. Members of the control group were selected from the pool of patients referred to non cardiac clinics. Data concerning name, age, sex, patient and family history of IHDs, and presence of risk factors such as diabetes, hypertension, smoking and hyperlipidemia were collected and recorded for patients and controls. More clinical information were obtained for AMI cases as electrocardiogram (ECG), cardiac enzyme values and cardiac catheterization results. For each AMI case, 2 blood samples were collected within 6 hours of admission and after 24-hours, in K3 ethylenediaminetetraacetic acid (EDTA) for lymphocyte immunophenotyping and blood group determination and in plain tubes for troponin I measurement. Whenever possible, a third K3 EDTA blood sample was collected before patient's discharge for lymphocyte immunophenotyping (on average after 7-10-days after admission). Only one blood sample was collected from each control subject and divided into 2 tubes, a tube containing K3EDTA and a plain tube.

Study protocol. Lymphocyte immunophenotyping. Lymphocyte immunophenotyping was performed by a flow cytometer (FACSort, Becton Dickinson California, United States of America) using SimulSET software and Simultest™ monoclonal antibodies (mAb). The following conjugated mAbs were used: CD45/CD14 for the establishment of an optimal lymphocyte gate, Simultest™ Control γ1/γ2a as a negative control, CD3/CD19 for the detection of T and B lymphocytes, CD3/CD4 for the detection of helper T lymphocytes, CD3/CD8 for the detection of cytotoxic T lymphocytes and CD4/CD8 to detect helper and cytotoxic T lymphocytes. The erythrocyte-lysed whole blood procedure was used. Briefly, to 100 μL of whole blood, 20 μl of anti-CD mAb were added followed by incubation for 15-30 minutes at room temperature before the addition of 2.0 ml of lysing solution and incubation for 10 minutes at room temperature. The mixture was then centrifuged at low speed (1500 rpm) for 5 minutes and the supernatant was removed. The cells were washed in 0.15 M phosphate buffered saline (pH 7.2) and resuspended in 0.5 ml of 1% paraformaldehyde for flow cytometric acquisition and analysis. The flow cytometer was calibrated daily according to a standard procedure. Samples were analyzed, and lymphocyte percentages were calculated using SimulSET software. At least 2000 lymphocytes were counted, and results were expressed as a percentage of the 2 tested CD markers in the lymphocyte analysis gate.

Cardiac troponin I (cTnI) measurement. Blood samples in plain tubes were allowed to clot, then centrifuged at 3000 rpm for 10 minutes, and serum was aspirated and kept frozen in aliquots at –70°C until tested. Specimens were assayed in batches within 2 hours of thawing. Cardiac troponin I measurement was performed using Microparticle Enzyme Immunoassay (AxSYM, Abbott laboratories, Illinois, USA). Each AxSYM cTnI assay kit was calibrated according to a standard procedure. The sample volume required to perform cTnI test on the AxSYM system was 220 μl and if dilution was necessary, an additional volume of 170 μl was added. If the value of cTnI was above 50 ng/ml, an automated 1:10 dilution was performed.

Rh and minor blood group phenotyping. Red blood cell phenotyping was performed using the Gel test (DiaMed ID™ Microtyping System, Cressier, Switzerland). Briefly, for Rh, K, P_1, Le^a, Le^b, Lu^a, Lu^b, k, Kp^a, Kp^b phenotyping, a 5% red cell suspension was prepared in bromelin solution and incubated for 10 minutes at room temperature except for Rh ID-Cards which were incubated at 37°C. Ten microliters of this suspension were dispensed in each microtube. The cards were then centrifuged for 10 minutes in DiaMed MTC-ID centrifuge and read by DiaMed-ID reader. For M, N, S, s, Fy^a and Fy^b phenotyping, a 0.8% red cell suspension was prepared in low ionic strength saline (LISS), and 50 microliters of this suspension were dispensed in each microtube, followed by the

Table 1 - Percentages of lymphocyte subsets in controls and in patients with acute myocardial infarction after 24 hours of admission and before discharge.

Parameter	Mean ± SD Controls n=45	Patients (24 h) n=45	Patients (before discharge) n=34
CD19%	10.47 ± 4.15	*14.04 ± 7.89	**12.95 ± 5.60
CD3%	75.02 ± 6.52	*70.22 ± 10.68	71.97 ± 8.67
CD4%	44.40 ± 4.91	*36.89 ± 9.45	+43.32 ± 6.99
CD8%	29.00 ± 5.91	*33.36 ± 8.39	+28.24 ± 7.56
CD4/CD8	1.6200 ± 0.4248	*1.1896 ± 0.5200	+1.6562 ± 0.5172

* compared with control *;*P*<0.02
** compared with control **;*P*<0.05
+ compared with first day +;*P*<0.02

Table 3 - Cardiac troponin levels in patients with acute myocardial infarction within 6 hours and at 24 hours after admission and cardiac troponin levels in non QWAMI and QWAMI.

Parameter	Mean ± SD cTn (mg/ml)
Control (n=45)	0.0 + 0.00
Patients within 6 hours* (N=45)	36.22 ± 88.24
Patients at 24 hours* (N=45)	263.18 ± 166.56
QWAMI** (N=39)	282 ± 167.18
Non QWAMI** (N=6)	138 ± 100.65

*P<0.001, **P<0.05
cTn - cardiac troponin

Table 2 - Comparison of the percentage of lymphocyte subsets in patients according to outcome of the acute myocardial infarction.

Parameter	Mean ± SD Alive n=39	Expired (n=6)
CD19%	13.46 ± 6.87	17.83 ± 13.03
CD3%	71.64 ± 8.56	61.00 ± 18.13
*CD4%	38.74 ± 8.14	24.83 ± 9.00
CD8%	33.21 ± 8.12	34.33 ± 40.76
*CD4/CD8	1.2590 ± 0.5146	0.7383 ± 0.2923

*P<0.02

Table 4 - Correlation between lymphocyte subsets and troponin 1 in patients with acute myocardial infarction after 24 hours admission.

Correlation	CD1%	CD%	CD4%	CD%	CD4/CD8
Sig. cTn1 2 tailed	0.339	0.115	0.002**	0.283	0.02*
Pearson cTn1 correlation	0.146	-0.239	-0.450**	0.163	-0.345*

*P<0.001, **P<0.05
cTnI - cardiac troponin

addition of 50 µl of the appropriate anti-sera. Cards were then incubated for 10 minutes at room temperature, centrifuged for another 10 minutes, and reactions were read by the ID-reader.

Statistical analysis. The statistical package for social sciences 7.5 software was used (SPSS, Inc. USA). Quantitative data were expressed as mean and standard deviation. Comparisons between groups were performed by the 2 tailed Student's t-test for independent samples, and comparisons within group and changes over time were performed by the 2 tailed Student's t-test for paired samples correlation. Coefficient of correlation was determined by Pearson's correlation method. Probability values less than 0.05 were considered significant. Analysis of variance was used to test the hypothesis that several means are equal, and if not to determine which means differ. Scheffe test was used to perform simultaneous joint pairwise comparisons for all possible pairwise combinations of means.

Results. **Table 1** shows the mean and standard deviation values of lymphocyte subsets in patients with AMI after 24 hours of admission and before discharge as compared to those in the control group. There was a statistically significant difference in all lymphocyte subsets measured after 24 hours. Percentages of $CD19^+$ as well as $CD8^+$ cells were significantly higher in patients with AMI than in controls, whereas $CD3^+$ and $CD4^+$ cell percentages and the $CD4^+/CD8^+$ ratio were significantly lower in patients with AMI than in controls (P value <0.02). The percentages of $CD19^+$ and $CD3^+$ cells did not differ significantly before discharge, while the $CD4^+$ cell percentage and the $CD4^+/CD8^+$ ratio increased significantly before discharge as compared to those after 24 hours of admission. The percentage of $CD8^+$ cells, on the other hand, was significantly lower before discharge than after 24-hours of admission. These subset percentages measured before discharge were comparable to those in controls except for the percentage of $CD19^+$ cells which remained significantly higher than that in the control group (P<0.05). The percentage of $CD4^+$ cells and the $CD4^+/CD8^+$ ratio in patients who expired of AMI were significantly lower than those who survived the attack (P<0.02). Differences in $CD19^+$ cells, on the other hand, were statistically

Table 5 - Percentages of lymphocytes subsets in patients with acute myocardial infarction having troponin levels of <400 ng/ml and in patients with acute myocardial infarction having troponin levels of ≥400 ng/ml.

Parameter	Mean ± SD Tn1 <400 n=33	Tn1 >400 n=12
CD19%	13.88 ± 7.13	14.50 ± 10.05
CD3%	72.21 ± 8.79	64.75 ± 13.67
**CD4%	40.06 ± 7.80	28.17 ± 8.2
CD8%	32.15 ± 8.30	36.67 ± 8.05
**CD4/CD8	1.3382 ± 0.5135	0.7808 ± 0.2571

* $P<0.05$, ** $P<0.001$
TnI - troponin

Table 6 - Correlation between the percentage of lymphocyte subsets after 24 hours of admission and before discharge and the number of vessels diseased.

Time	Correlation	CD19%	CD3%	CD4%	CD8%	CD4/CD8 ratio
At 24 hours after admission (n=31)	Sig. cath 2-tailed	0.543	0.469	0.538	0.566	0.695
	Pearson cath correlation	-0.114	-0.135	-0.115	0.107	-0.73
Before discharge (n=26)	Sig. cath 2-tailed	0.329	0.745	0.771	0.441	0.693
	Pearson cath correlation	-0.199	0.067	-0.059	0.158	-0.081

Correlation is significant at the 0.05 level (2-tailed)

insignificant (**Table 2**). Lymphocyte subsets did not differ significantly between patients with Q-wave AMI and those with non Q-wave AMI as measured after 24 hours of admission. No statistically significant differences in lymphocyte subsets were observed when patients were compared according to sex or according to the presence of risk factors for IHD including; patient history of IHD, family history of IHD, hypertension, diabetes mellitus, smoking and hyperlipidemia. As demonstrated in **Table 3**, cTnI levels were significantly higher in patients with AMI within 6 and at 24 hours after admission as compared to those in controls. Moreover, there was a significant increase in cTnI levels in patients with AMI measured at 24 hours of admission as compared to cTnI levels measured within 6 hours of admission. ($P<0.001$). **Table 3** demonstrates as well statistically significant higher cTnI levels in patients with Q-wave AMI as compared to patients with non Q-wave AMI ($P<0.05$). A highly significant negative correlation was demonstrated between cTnI levels and the percentage of $CD4^+$cells as well as the $CD4^+/CD8^+$ ratio in patients with AMI (**Table 4**). Moreover, patients with AMI whose cTnI levels were ≥400 ng/ml had significantly lower percentages of $CD3^+$ and $CD4^+$ cells as well as lower $CD4^+/CD8^+$ ratio as compared to patients with AMI whose cTnI levels were <400 ng/ml (**Table 5**). When catheterization findings were analyzed in view of the results of lymphocyte immunophenotyping, no significant correlation was found between the percentages of lymphocyte subsets measured 24 hours after admission and before discharge and the number of vessels diseased (**Table 6**). A highly significant association ($P<0.001$) between the $Le(a^-b^-)$ phenotype and AMI was observed (**Table 7**) as 77.8% of patients with AMI had this phenotype as compared to 44.4% of the controls.

Discussion. The results of this study demonstrate that lymphocyte subpopulations undergo, at least, quantitative alterations in AMI. These changes which involve $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ cells and the $CD4^+/CD8^+$ ratio may be related to the pathogenesis of the disease or its complications. This is in agreement with several reports that have implicated immune responses, particularly cellular ones, in various vascular and cardiac disorders, such as atherosclerosis,[23] autoimmune myocarditis,[24] congestive cardiomyopathy[11] post cardiac surgery[25] and AMI.[5] Results of this study with respect to changes of lymphocyte subsets in AMI support the findings of Blum et al,[4] Syrjala et al,[5] Kuroki et al[7] and Che et al,[9] but appear in contrast with those of Dimitrijevic et al[12] and Tsuchihashi et al.[10] The significant increase in the percentage of $CD19^+$ cells demonstrated in patients with AMI throughout hospitalization may be explained on the basis of

Table 7 - Distribution of patients and controls according to blood groups other than the ABO system.

Blood group	Control n=45 n (%)		Patient n=45 n (%)	
D	39	(87.6)	41	(91.1)
C	36	(80)	38	(84.4)
C	26	(57.8)	32	(71.1)
E	4	(8.9)	8	(17.8)
E	44	(97.8)	45	(100)
P1	31	(68.9)	34	(75.6)
*Le (a^-b^-)	20	(44.4)	35	(77.8)
Le (a^-b^+)	9	(20)	20	(44.4)
Le (a^+b^+)	0	(0)	5	(11.1)
Le (a^+b^+)	1	(2.2)	0	(0)
Lu^a	2	(4.4)	0	(0)
Lu^b	45	(100)	45	(100)
Fy^a	22	(60)	23	(51.1)
Fy^b	32	(71.1)	25	(55.6)
Kp^a	4	(8.9)	1	(2.2)
Kp^b				
Jk^a	45	(100)	45	(100)
Jk^b	33	(73.3)	35	(77.8)
K	0	(0)	0	(0)
Kell	44	(97.8)	45	(100)
M	3	(6.7)	5	(11.1)
	18	(40)	27	(60)
N	30	(66.7)	28	(62.2)
S	20	(44.4)	24	(53.3)
S	42	(93.3)	39	(86.7)

*P<0.001

activation by a triggering event in AMI, such as the release of sequestered antigens. Moreover, such patients may have had high B cell counts prior to the onset of AMI. Dimitrijevic et al[12] and Che et al[9] reported a significant increase in the percentage of B cells in patients by the 14th day after the onset of AMI as compared to the controls. They attributed this increase to the release of sequestered antigens from the necrotic myocardial tissue. To the contrary, Tsuchihashi et al[10] could not demonstrate a significant difference in the percentage of B cells between patients and controls. An interesting finding of this study was that patients with very low $CD4^+$ cell percentages and $CD4^+/CD8^+$ ratio either had complications or died, indicating that such changes may be considered as prognostic markers in AMI. The immunologic changes that accompany or follow the onset of AMI, or both, seem to be related to the disease itself since they were demonstrated to be independent of risk factors for AMI. Certain factors associated with AMI may act to depress cell-mediated immunity. There is an increasing body of evidence to suggest that acute stress increases plasma cortisol levels, which function to decrease T lymphocyte percentage.[6,26] Similarly, Syrjala and associates[5] related the inverted $CD4^+/CD8^+$ ratio in AMI observed on admission to the stress reaction. Another factor that may operate to induce cell-mediated suppression in AMI is the administration of morphine in the treatment of pain as Navarro et al[8] reported that the use of morphine in anesthesia leads to a decrease in the percentage of T helper cells and an increase in the percentage of T cytotoxic cells. Moreover, the use of streptokinase as a thrombolytic agent in AMI, was reported by Blum and Shohat[27] to induce CD4-lymphopenia and a low $CD4^+/CD8^+$ ratio. The results of the present study support the previously published reports regarding the benefits of cTnI measurements in confirming the diagnosis of AMI.[17,18,28-31] It was also demonstrated that patients with non Q-wave AMI had significantly lower serum levels of cTnI as compared to patients with Q-wave AMI. Despite the fact that cTnI levels are not widely utilized to assess the extent of cardiac damage and severity of disease, nor recommended for that purpose, a positive correlation seems to exist in this regard. Furthermore, this study demonstrated a highly significant negative correlation between serum levels of cTnI and the percentages of $CD4^+$ cells as well as the $CD4^+/CD8^+$ ratio. Kuroki et al[7] demonstrated a weak negative correlation between the $CD4^+$ cell percentages and serum level of Creatin in Kinase (CK). Similarly, Blum et al[4] reported that patients with low $CD4^+$ cell counts and low $CD4^+/CD8^+$ ratio on admission had larger mass destruction as reflected by CK levels. On the contrary, Tsuchihashi et al[10] reported no significant correlation between the percentages of lymphocyte subsets and infarct size. The correlation between the percentage of $CD4^+$ cells and the $CD4^+/CD8^+$ ratio and serum cTnI levels during AMI has not been previously studied. It was observed that patients with cTnI levels of less than 400 ng/ml had significantly higher percentages of $CD3^+$ and $CD4^+$ cells and a higher $CD4^+/CD8^+$ ratio than those with cTnI level of 400 ng/ml or more. This may explain the observation made in this study that higher percentages of $CD3^+$ and $CD4^+$ cells were found in patients with non Q-wave AMI than patients with Q-wave AMI. In fact, this figure (400ng/ml) has been chosen for comparison in this study as of the observation that most patients who had extensive AMI, who developed complications such as, atrial fibrillation, left bundle branch block, pulmonary edema and reinfarction or who died of AMI had cTnI levels of >400 ng/ml. The observation that high serum levels of cTnI are predictive of a poor outcome is consistent with the report of Lucia et al.[32] Moreover, there was no correlation between changes in lymphocyte subsets and the number of vessels diseased. A highly significant association was demonstrated in this study between the Le (a^-b^-) phenotype and AMI. Moreover, the presence of Le (a^-b^+) phenotype seems to have a protective effect from AMI, as it was significantly higher among controls, indicating an association between the lack

of Le^b and the occurrence of AMI. This is in agreement with the previously published reports by Hein et al[20,21] and Ellisson et al,[18] where the Le (a^-b^-) phenotype was associated with obesity, insulin resistant diabetes mellitus, alcohol consumption and higher serum levels of triglycerides all of which are risk factors for coronary heart disease.

In conclusion, the results of this study demonstrate that alterations of lymphocyte subsets responsible for both cell mediated and humoral immunity take place in AMI. Moreover, the percentage of $CD4^+$ cells as well as the $CD4^+/CD8^+$ ratio can be considered as important determinants of disease severity and outcome and thus may be utilized with cTnI levels as prognostic markers in AMI.

References

1. Tunstall-Pedoe H, Kuulasmaa K, Annouyel D. The WHO MONICA project. Myocardial Infarction and Coronary deaths in the World Health Organization MONICA project. ***Circulation*** 1994; 90: 583-612.
2. Hansson GK. Immune and Inflammatory Mechanisms in the Development of Atherosclerosis. ***Br Hear J*** 1993; 69 (suppl): S38-S41.
3. Van der Wal, AC, Das, PK, van der Loos. Atherosclerotic Lesions in Humans. In situ Immunophenotypic Analysis Suggesting an Immune Mediated Response. ***Lab Invest*** 1992; 61: 166-170.
4. Blum A, Sclarovsky S, Rehavia E. Levels of T-Lymphocyte subpopulations, Interleukin-1B, and Soluble Interleukin-2 Receptor in Acute Myocardial Infarction. ***Am Heart J*** 1994; 127: 1226-1230.
5. Syrjala H, Surcel HM, Ilonen J. Low CD4/CD8 T Lymphocyte ratio in Acute Myocardial Infarction. ***Clin Exp Immunol*** 1991; 83: 326-328.
6. Dhabhar FS, Miller AH, McEwan BS. Effects of Stress on Immune Cell Distribution Dynamics and Humoral Mechanisms. ***J Immunol*** 1995; 154: 5511-5527.
7. Kuroki S, Miyahara K, Uematsu T. Immunological Aspects in Patients with Acute Myocardial Infarction. ***Jpn Circ J*** 1993; 57: 37-46.
8. Navarro M, Lozano R, Larrad L. Variation in T Helper Cell/T Cytotoxic- Suppressor Cell Index During Cardiac Operation. ***J Thorac Cardiovasc Surg*** 1988; 96: 962-966.
9. Che J, Zhu L, Li K, Chen S. Alteration of the Percentage of Lymphocytes in Patients with Acute Myocardial Infarction and Clinical Evaluation. ***Chin Med J Engl*** 1995; 108: 784-786.
10. Tsuchihashi M, Sakaguchi Y, Nakamura M. Two color Flow Cytometry Analysis of Lymphocyte Subsets in Patients with Acute Myocardial Infarction and Post Acute Myocardial Infarction Syndrome [abstract]. ***J Cardiol*** 1995; 26: 69-79.
11. Lowry PJ, Gammage MD, Gentle TA. Suppressor T Lymphocyte Function in Patients with Congestive Cardiomyopathy. ***Br Heart J*** 1987; 57: 458-461.
12. Dimitrijevic M, Vasiljevic Z, Vuckovic-Dekic L. The Involvement of Immune Reactions in Cardiac Damage During Acute Myocardial Infarction: Role of Cell Mediated Immune Response. ***Panminerva Med*** 1997; 39: 85-94.
13. Kaufman HS, Kvitash VI. Immunologic Abnormalities Associated with Acute Ischemic Heart Diseases (a pilot study). ***Ann Allergy*** 1989; 63: 287-290.
14. Van Offel JF, Bosmans JN, Vrints C. Immunological Abnormalities in Ischemic Heart Diseases. ***Ann Allergy*** 1985; 55: 296-297.
15. Mair J, Wagner I, Morass B. Cardiac Troponin I Release Correlates with Myocardial Infarction Size. ***Eur J Clin Biochem*** 1995; 33: 869-872.
16. Tanaka H, Abe S, Yamashita T. Serum Levels of Cardiac Troponin I and Troponin T in Estimating Myocardial Infarct Size Soon after Reperfusion. ***Coron Artery Dis*** 1997; 8: 433-439.
17. Del Rey JM, Madrid AH, Valino JM. Cardiac Troponin I and Minor Cardiac Damage: Biochemical Markers in a Clinical Model of Myocardial Lesions. ***Clin Chem*** 1998; 44: 2270-2276.
18. Ellison RC, Zhang Y, Mayers RH. Lewis Blood Group Phenotype as an Independent Risk Factor for Coronary Heart Disease (The NHLBI Family Heart Study). ***Am J Cardiol*** 1999; 83: 345-348.
19. Medalie JH, Levene C, Papier C. Blood Groups, Myocrdial Infarction and Angina Pectoris among 10,000 Adult Males. ***N Engl J Med*** 1971; 285: 1348-1353.
20. Hein HO, Sorensen H, Suadicani P. Lewis Blood Group -a New Genetic Marker of Ischaemic Heart Disease. ***J Intern Med*** 1992; 232: 481-488.
21. Hein HO, Sorensen H, Suadicani P. Alcohol Consumption, Lewis Phenotypes, and Risk of Ischaemic Heart Disease. ***Lancet*** 1993; 341: 392-396.
22. Chaudhary R, Shukla JS. Association of Lewis Blood Group with Ischemic Heart Disease. ***Indian J Med Res*** 1999; 109: 103-104.
23. Van der Wal AC, Becker AE, van der Loos CM. Site of Intimal Rupture or Erosion of Thrombosed Coronary Atherosclerotic Plaque is Characeterized by an Inflammatory Process Irrespective of the Dominant Plaque Morphology. ***Circulation*** 1994; 89: 36-44.
24. Rose NR, Neumann DA, Herskowitz A. Autoimmune Myocarditis: Concepts and Questions. ***Immunol Today*** 1991; 12: 253-255.
25. Habermeh1 P, Knuf M, Kampmann C, Mannhardt W, Schranz D, Kuroczynski W et al. Changes in lymphocyte subsets after cardiac surgery in children. ***Eur J Pediatr*** 2003; 162: 15-21.
26. Khansari DN, Murgo AJ, Faith RE. 1990. Effects of Stress on the Immune System. ***Immunol Today*** 1990; 11: 170-175.
27. Blum A, Shohat B. CD4 Lymphopenia Induced by Streptokinase. ***Circulation*** 1995; 91: 1899.
28. Mair J, Wagner I, Puschendorf B. Cardiac troponin I to Diagnose Myocardial Injury. ***Lancet*** 1993; 314: 838-839.
29. Apple FS, Falahati A, Paulsen PR. Improved Detection of Minor Ischemic Myocardial Injury with Measurement of Serum Cardiac Troponin I. ***Clin Chem*** 1997; 43: 2047-2050.
30. Apple FS, Christenson R, Valdes R. Simultaneous Rapid Measurements of Whole Blood Myoglobin, Creatinine Kinase MB, and Cardiac Troponin I by the Triage Cardiac Panel for the Detection of Myocardial Infarction. ***Clin Chem*** 1999A; 45: 199-205.
31. Apple FS, Maturen AJ, Mullins RE. Multicenter Clinical and Analytical Evaluation of the AxSYM Troponin-I Immunoassay to Assist in the Diagnosis of Myocardial Infarction. ***Clin Chem*** 1999B; 45: 206-212.
32. Lucia P, Coppola A, Manetti LL, Sebastiani ML, Colliardo A, Cerroni F et al. Cardiac troponin 1 in acute coronary ischemic syndromes. Epidemiological and clinical correlates. ***Int J Cardiol*** 2001; 77: 215-222.