IMMUNOLOGICAL ASPECTS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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In order to elucidate the immunological aspects of acute myocardial infarction (AMI), we studied lymphocyte subpopulations, immunoglobulin levels, and natural killer (NK) cell activity in 21 patients serially after admission within 24 h of AMI onset. The percent T cells, T cell count, and percent CD4-positive cells were significantly decreased on the 1st hospital day, compared to days 7 and 28. The CD4/CD8 ratio on the 1st day was also significantly lower than on day 7, and was significantly lower than that of normal subjects. Natural killer (NK) cell activity and serum immunoglobulin G (IgG) levels showed substantial decreases each test day, compared with those in normal subjects. However, there were no significant serial changes in the percent B cells, the B cell count, or in the serum IgG, IgA, or IgM levels. Thus, not only T cell function, but also immunoglobulin levels and NK cell activity were depressed in the acute stage of myocardial infarction. Therefore, active measures should be taken to prevent infection in the acute stage of myocardial infarction in which invasive procedures such as insertion of indwelling catheters are often necessary.

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IT has been reported that T cell function, immunoglobulin levels, and natural killer (NK) cell activity are inhibited following non-infectious tissue injuries such as occur during surgery and in cases of trauma or burn^{1–6}. This suggests that a non-infectious tissue injury may derange the protective mechanisms for infection, leaving the patient highly susceptible to infection. The etiology of this immunological disorder may be related to the (physical) stress-induced secretion of endogenous steroids and catecholamines^{2,6,7}.

While myocardial infarction is considered to be a non-infectious tissue injury, the

immunological aspects of this acute stage of disease are not known. Few studies have reported on T cell function and NK cell activity in this regard^{8–13}. The present study serially examined three different immunological parameters in the acute stage of myocardial infarction, to determine their ability to protect the acute myocardial infarction patient from infection.

SUBJECTS AND METHODS

Patients

Twenty-one acute myocardial infarction (AMI) cases (13 males and 8 females) admitted to our hospital within 24 h of onset, and who survived over one month (from August, 1988 to July, 1989), were evaluated (MI group). The mean age of the MI group was 66.1 ± 9.3 years (range 48 to 81 years). Pa-

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TABLE I CLINICAL CHARACTERISTICS OF THE 21 PATIENTS

No	Age	Sex	Infarct site	Forrester subset	Σ CPK (IU)	Intervention Therapy	Complication	Outcome
1	81	F	A-S	—	1038	—	VF	Alive
2	58	F	A-S	1	768	PTCR	—	Alive
3	66	M	A-S	2	1460	—	—	Alive
4	69	F	A-S	1	2789	PTCR	—	Alive, CABG
5	53	F	A-S	2	4349	PTCR	—	Alive
6	69	M	A-S	1	7966	PTCR	—	Alive
7	53	M	A-S	1	1035	PTCR	—	Alive, PTCA
8	48	M	A-S	1	3325	PTCR	—	Alive
9	71	F	A-S	1	2602	—	—	Alive
10	71	F	A-S	1	1710	PTCR	—	Alive, PTCA
11	69	M	Inf	1	448	PTCR	—	Alive
12	62	M	Inf	1	9678	—	—	Alive, CABG
13	57	M	Inf	1	2747	—	—	Alive, CABG
14	77	M	Inf	3	1807	—	—	Alive
15	77	M	Inf	3	2382	PTCR	RV infarct	Alive
16	79	F	Inf	3	7279	—	RV infarct	Alive
17	66	M	Inf	1	1793	PTCR	—	Alive
18	70	M	Post	—	3012	—	—	Alive
19	62	M	Post	2	2191	PTCR	—	Alive
20	76	F	Post	4	3315	PTCR, IABP	—	Alive
21	54	M	Post	2	2853	PTCR, IABP	—	Alive, CABG

M: male; F: female; A-S: antero-septal; Inf: inferior; Post: posterior; CPK: creatine phosphokinase PTCR: percutaneous transluminal coronary recanalization; IABP: intra-aortic balloon pumping; RV infarct: right ventricular infarction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft

tients with active pulmonary tuberculosis, autoimmune diseases, and severe infectious diseases were excluded from the study. Table I lists the clinical characteristics of these patients. The control group (group C) consisted of 21 healthy subjects matched for age and sex to the MI group (12 males and 9 females, aged 50 to 76 years, mean $65/8 \pm 6.2$).

Immunological Parameters

The following immunological parameters were determined in the peripheral venous blood: white blood cell count (WBC), lymph cell count, lymphocyte subpopulation indices (such as: the percent T cells, T cell count, percent CD3-positive cells, percent CD4-positive cells, percent CD8-positive cells, CD4/CD8 ratio, percent B cells, B cell count, and percent CD20-positive cells), immunoglobulin indices, (such as serum IgG, IgM and IgA levels), NK cell activity, and large granular lymph (LGL) cell count (which is known to have NK cell activity).

METHODS

Blood samples were collected from the MI group on the 1st, 7th, and 28th days. Sampling was usually performed in the early morning following an evening fast, except for the 1st day. Group C, was sampled once, at the same time as the MI group, and the results served as the normal control values. Examination of each parameter was carried out according to the following methods: Two ml of heparinized peripheral blood was collected from the peripheral vein and the WBC count was calculated with a Sysmex E-300 (Toa Medical Electronics). Smear specimens were prepared on a slide glass, stained with Wright-Giemsa, and the WBC parameters were analyzed. The peripheral lymph cell count was calculated by multiplying the peripheral WBC count by the proportion of lymph cells. For the percent T and B cell measurements, $5 \mu\text{l}$ each of the monoclonal antibodies Fluorescein (FITC)-conjugated CD20 (NU-B2: Nichirei) and Phycoerythrin (PE)-conjugated CD2 (T11: Coulter Clone) were added to $100 \mu\text{l}$ of heparinized

Fig.1. Serial changes of WBC's and lymph cells in patients with acute myocardial infarction. The WBC count normalized with time, but there was no significant change in the lymph cell count. WBC: white blood cell

Fig.2. Serial changes of the percent T cells and B cells in patients with acute myocardial infarction. Although the percent B cells was not significantly changed, the percent T cells on the 1st day was significantly lower compared to other hospital days and the control group.

peripheral blood. After 15 min of incubation at room temperature, a lysing reagent was added and the samples were incubated for 15 min at room temperature. The samples were washed with a phosphatebuffered saline (PBS) and resuspended in 1 ml of PBS. An analysis of flow cytometry was performed using a flow cytometer (FACScan: Becton Dickinson) with the scatter gates set for lymph cell fraction. CD2- positive and CD20-negative cells were considered to be T cells. CD2-negative and CD20-positive cells were considered to be B cells¹⁴. The percents of CD3-positive, CD4-positive, and CD8-positive cells were determined with a flow cytometer using FITC-labelled antibodies (Leu4, Leu3a, Leu2a; Becton Dickinson).

Serum IgG, IgM, and IgA levels were analyzed on an automatic analyzer (7150; Hitachi), using antisera IgG, IgM, and IgA (Hoechst Japan), with immunochlotimetry. NK cell activity was determined according to the following methods:¹⁰

Effector cells: Mononuclear cells, isolated using a Ficoll Isopaque gradient centrifugation, were collected in 5 ml of saline and washed three times with RPMI 1640 supplemented with 10% fetal calf serum (FCS). The mononuclear cells were then resuspended in the same medium at a concentration of 2×10^6 cells/ml.

Target cells: The human leukemia cell line K562 was maintained in continuous

TABLE II RESULTS OF IMMUNOLOGICAL PARAMETERS

	Group MI			Group C
	1st day	7th day	28th day	
WBC (/mm ³)	10730±3540 [‡]	8050±2620 ^{*‡}	5810±1510 ^{***}	5030±1050
Lymph (/mm ³)	1670±950	2190±710	2100±620	2120±610
% T-cell	75.7±6.9 [‡]	79.6±4.4 [*]	72.3±4.5 ^{**}	81.1±5.4
T-cell count (/mm ³)	1260±720 ⁺	1730±530 [*]	1720±470 [*]	1710±470
CD3 (%)	59.0±12.5 ⁺	68.7±8.9 ^{**}	68.9±8.8 ^{**}	65.9±7.1
CD4 (%)	36.2±11.8 [‡]	48.0±8.3 ^{***}	44.4±11.6 [*]	45.1±5.0
CD8 (%)	25.9±7.4 ⁺	22.3±6.4	25.4±6.7 ⁺	20.9±5.1
CD4/CD8 (%)	1.57±0.78 [‡]	2.37±0.91 ^{**}	1.98±1.06	2.28±0.59
% B-cell	12.5±0.78	11.7±4.8	9.7±4.6	10.5±4.7
B-cell count (/mm ³)	224±190	270±166	215±142	231±136
CD20 (%)	14.3±5.8	12.3±3.7	10.8±4.0	10.4±4.6
IgG (mg/dl)	1250±250 [‡]	1150±270 [‡]	1270±290 ⁺	1480±260
IgM (mg/dl)	125±60	124±62	132±69	138±52
IgA (mg/dl)	291±123	298±106	286±109	306±132
NK activity (%)	16.2±14.0 [‡] (20)	8.6±5.8 ^{*‡} (21)	11.0±6.2 [‡] (18)	30.9±12.2 (21)
LGL cell count (mm ³)	422±295 (14)	334±209 (16)	420±232 (14)	419±180 (21)

* compared with 1st day, *, $p<0.05$ **, $p<0.01$ ***, $p<0.001$

+ compared with control, +, $p<0.05$ ‡, $p<0.01$ ‡, $p<0.001$

MI: myocardial infarction, C: control, WBC: white blood cell, Lymph: lymph cell, NK: natural killer cell
LGL: large granular lymph, Parenthesis: number of patients

culture in RPMI 1640 supplemented with 10% heat-inactivated FCS. Na²⁵¹CrO₄ (0.1 ml of 100 μCi; New England Nuclear, Boston, Mass, USA) was added to 4×10⁶ target cells in 0.1 ml solution. The cells were incubated with the isotope for 1 h at 37 °C in 5% CO₂. The labelled cells were then washed three times with RPMI 1640 supplemented with 10% FCS. The cell pellet was then resuspended in the same medium at a concentration of 2×10⁵ cells/ml.

Cytotoxic assay: The 50 μl suspension of labelled target cells was mixed with 100 μl of effector cells suspension and 50 μl of RPMI 1640, supplemented with 10% FCS in 96 microplates with well-rounded bottoms. After incubation for 4 h at 37 °C in 5% CO₂, each supernatant was collected using a Skatron Supernatant Collection System (Skatron Co., Lier, Norway). The radioactivity of ⁵¹Cr in the supernatant was assessed using an LKB gamma counter. The percent cytotoxicity was calculated using the following formula:

$$\% \text{ Cytotoxicity} = \frac{\text{Experimental release (cpm)} - \text{Spontaneous release (cpm)}}{\text{Maximum release (cpm)} - \text{Spontaneous release (cpm)}} \times 100$$

and Nk cell activity was measured in triplicate at a 20:1 effector/target (E/T) cell ratio.

The LGL cell count was calculated by multiplying the peripheral lymph cell count by the proportion of LGL that appeared as large lymph cells with azurophilic cytoplasmic granules.

In the MI group, creatine kinase (CPK), aspartate transaminase (GOT), lactate dehydrogenase (LDH), and hydroxybutyrate dehydrogenase (HBD) were measured serially in all subjects. Special care was taken to measure creatine kinase every 6 h for the first 24 h. The size of the infarction was estimated by calculating Σ CPK.¹⁵ The hemodynamic severity of the AMI was determined according to Forrester's classification with an indwelling thermo-dilution catheter. The catheter was placed in the

Fig.3. Attitudes of the percent CD4-positive and CD8-positive cells in patients with acute myocardial infarction. The percent CD4-positive cells on the 1st day was significantly lower compared with that on other hospital days and the control group. The percent CD8-positive cells on the 1st and 28th days was significantly higher than the control group, but showed no serial changes.

right heart of 19 subjects in group MI for three days during the acute stage.

Statistics

All values are presented as mean $\pm$ standard deviation, and statistical analyses were performed using the Student t test for the parallel comparison, and the paired t test for the within-subject comparison. The correlation between Σ CPK and Forrester's classification versus immunological parameters was obtained using a linear regression analysis. A p value of less than 0.05 was considered statistically significant.

Fig.4. The CD4/CD8 ratio after acute myocardial infarction. This parameter was significantly lower on the 1st day compared to the 7th day and the control group.

RESULTS

The results for all immunological parameters are shown in Table II. Peripheral WBC count was serially decreased and, in time, reached the normal range. There were no significant changes in the peripheral lymph cell count, and no significant difference was found compared with that of group C (Fig. 1). The percent T cells and T cell count on the 1st hospital day were significantly lower than those on the 7th and 28th hospital days. These measurements were significantly lower than those of group C. However, no remarkable changes were observed in the B cell measurements (Fig. 2). The values for the percent CD3-positive and CD4-positive cells were also lower on the 1st hospital day than on the 7th and 28th days. These measurements were also lower than those of group C (Table II, Fig. 3). While no serial changes were evident in the percent CD8-positive cells, these measure-

Fig. 5. Natural killer (NK) cell activity in patients with acute myocardial infarction. NK cell activity on the 1st day was higher than that on the 7th day, and was significantly lower in all series compared to the control group.

ments were significantly higher on the 1st and 28th hospital days than those of group C (Fig. 3).

The CD4/CD8 ratio was significantly lower on the 1st day, compared with that on the 7th day and compared to that of group C (Fig. 4). Although NK cell activity on the 1st hospital day was significantly higher, than that on the 7th day, it was always significantly lower than that of group C (Fig. 5). The LGL cell count did not change serially, and there was no significant difference in this parameter between the 2 groups (Fig. 6). The percent CD20-positive cells on the 1st hospital day was higher, than that on the 28th day, and this relatively high value was shown only on the 1st day (Table II). By contrast, serum IgG, IGM, and IgA levels did not change serially throughout the clinical course, and only serum IgG levels decreased significantly on each test day, compared to group C. There were no significant differences between the 2 groups for serum IgM and IgA levels (Fig. 7). In addi-

Fig. 6. The LGL cell count in patients with acute myocardial infarction. No significant serial changes and no significant differences were found compared to the control group. LGL: large granular lymph.

tion, no relationship between any immunological index and the infarct size (estimated by Σ CPK) or the hemodynamic severity (based on Forrester's classification) was revealed, although a weak negative correlation between Σ CPK and the percent CD4-positive cells was observed on the 1st day (Fig. 8).

DISCUSSION

Agrawal et al⁸ reported that low values in the percent T cells were found at the 1st week after AMI and that inversely high values were found at the 2nd and 3rd weeks. Further, these changes were reportedly not related to the site or extent of the infarction,

Fig.7. Immunoglobulin levels (IgG, IgA, and IgM) in patients with acute myocardial infarction. No significant serial changes were recognized in serum IgG, IgM, or IgA levels, but the serum IgG level in all series were showed a significant decrease compared to the control group.

Fig.8. The value of Σ CPK and ***the percent CD4-positive cells on the 1st day in patients with acute myocardial infarction. A weak negative correlation was recognized.

or to the presence of complications such as heart failure and arrhythmia. It was postulated that a high percent T cells value could be caused by helper T cell responses enhances by, myocardial antigens. It was also postulated that these were the results—but not the causes—of the myocar-

dial disorders.

Contrarily, Kaufman et al¹¹ reported that suppression of delayed-type dermal hypersensitivity responses and decreases in percent T cells measurements were found in infarction cases that died within one month of onset. Viral infection suppression of T

cell function and stress were suggested as possible causative factors. Moreover, Syrjala et al¹³ indicated that the CD4/CD8 ratio of AMI patients was lower on the 1st day, as compared to controls, but returned to normal on the 2nd day. However, Klarlund et al¹⁰ reported that NK cell activity was suppressed from the 1st day to the 6th week. According to this report, there were no significant changes in the LGL cell count, and depressed NK cell activity was induced by a dysfunction of the NK cells.

While there are many reports on the immune response⁸⁻¹³ including the reports on the suppression or activation of T cell function, there exists no comprehensive report regarding general immunity in the acute stage of myocardial infarction.

In the present study, abnormalities in T cell function were found in the test group in the early stage of infarction, and serum IgG levels were found to be low on every test day, as compared to group C. Meanwhile, no significant serial changes in the LGL cell count were shown in the MI group, and no significant difference was found between the two groups. However, NK cell activity was found to be depressed on all test days. These data suggest that there may be a dysfunction of the NK cells in these cases.

In addition, there was a weak negative correlation between Σ CPK and the percent CD4-positive cells on the 1st day, although no significant relationship was observed between the abnormalities of the other immunological parameters and the size or severity of the myocardial infarction. Thus, there were decreases of not only T cell function but also of immunoglobulin levels and NK cell activity in the acute stage of this disease. And these abnormalities were not closely related to the size and severity of the myocardial infarction.

The low percent of CD4-positive cells and the suppression of NK cell activity may be very important, since CD4-positive T cells are known to modify and control various immune responses including: the delayed hypersensitivity response, lymph cell transformation induced by mitogen or stimulation of antigen, the production of lymphokines, the differentiation and proliferation of cytotoxic T cells, and the synergic action of T cells to immunoglobulin productive B

cells.¹⁶⁻¹⁸ For this reason, it is suggested that a decrease in the percent of CD4-positive cells evokes both abnormal T cell function and defective immunoglobulin levels. However, it is well established that NK cells play an important protective role in the early phase of infection, because of their ability to inhibit certain oncocytes, and cells infected with virus, fungus, or bacteria, without stimulating antibodies.^{19,20} It is clear that the suppression of NK cell activity may damage a protective mechanism that is important in the early phase of infection.

According to reports¹⁻⁶ of changes in the immune response as a function of certain physical stresses (e.g. burns, traumas, and surgery), NK cell activity is suppressed under physical stress, and as stress increases, the suppression of NK cell activity is prolonged and both T and B cell levels decrease. The decrease in T cells is especially large.

Other reports suggest that an increase in stress-induced endogenous steroids plays a role in immune suppression.^{21,22} It has been reported that T cells decrease with steroid administration,²³⁻²⁵ and further, that there is a marked decrease in CD4-positive cells²⁶ and NK cell activity.²⁷ In the case of burn injuries, Aikawa et al² suggested that the prolonged secretion of catecholamines after the burn might play a role in T cell dysfunction.

Malec et al²⁸ reported that exogenous catecholamines increase the intracellular cyclic adenosine monophosphate (cAMP) and so inhibit NK cell activity. Reportedly, an inactivation of NK cell activity is caused by prostaglandin E₂²⁹ which inhibits T cell functioning during physical stress.³⁰ Ceremuzynski³¹ revealed that there are increases in glucocorticoids and catecholamines that damage the cardiac muscle in AMI. It is believed that an accelerated secretion of endogenous catecholamines and steroids plays a role in the immunological abnormalities observed during physical stress.

In the present study, serum IgG was the only immunoglobulin that decreased. And the deterioration of NK cell activity and serum IgG levels continued until the 28th hospital day. The reason for these changes remains uncertain. The findings of the

present study, combined with a review of previous research, suggest that the following process may account for the abnormalities observed in the immune response after physical stress: AMI-induced physical stress increases endogenous catecholamine levels, which, in turn, increase intracellular cAMP levels. Concurrently, prostaglandin E₂, activated by stress and enhanced by the increase in cAMP levels, inhibits both T cell function and NK cell activity. Helper T cell dysfunction, then decreases the coordination responses by helping B cells to develop into antibody-producing cells. This cascade of changes seems to decrease T cell function, immunoglobulin levels, and NK cell activity during AMI. It appears, therefore, that active treatment is required to prevent infections in the acute stage of myocardial infarction, particularly since surgical procedures such as the insertion and indwelling of catheters may cause secondary infections.

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