Since Ader and Cohen found conditioned immunosuppression in the course of taste aversion conditioning, attention has been paid to psychoneuroimmunological studies, which have advanced to studies on the association between psychological stress and immunity, in turn leading to discussion about the role of stress in the growth of tumors. It has been suggested that the immune system serves an immunosurveillance. If psychological stress interferes with this function, a tumor may be allowed to grow to a size that immune system can no longer deal with easily. In recent years, exercise and training have been studied as factors affecting immune responses. We have performed sports rehabilitation for patients with coronary heart disease from the aspect of exercise psychology. As part of studies on the effects, especially the preventive effects, of exercise and psychological factors on cardiovascular diseases, the association between psychological tendencies and immune response was evaluated in patients with coronary heart disease who were receiving exercise therapy. The Pearson’s product-moment correlation coefficients between natural killer (NK) cell activity and various psychological scales were obtained. For the Moodsley Personality Inventory, NK cell activity had a significant positive correlation with the extraversion scale and a significant negative correlation with the neuroticism scale. NK cell activity also had a significant positive correlation with the playful humor scale and a significantly negative correlation with the Self-rating Depression Scale. The positive correlation of NK cell activity with the extraversion scale and the humor scale and its negative correlation with the neuroticism scale suggest an association between a positive-feeling tendency and high NK cell activity. The negative correlations of NK activity with the depression scale and neuroticism scale indicate that decreased or excessive expression of feelings inhibits NK cell activity. Thus, high NK activity appears to be associated with optimal expression of feelings. (Jpn Circ J 1999; 63: 704–709)

Key Words: Cardiac sport rehabilitation; Coronary heart disease; Immune function; Psychological factors

Methods

Subjects

The subjects were 37 patients (19 males, 18 females) with a mean age of 67.3±5.9 years who were receiving cardiac sports rehabilitation. Thirty patients had coronary heart diseases (CHD) (19 with myocardial infarction, 11 with angina pectoris). Three patients had 3-vessel disease, 8 patients had 2-vessel disease, and 19 patients had 1-vessel disease. The remaining 7 had more than one cardiac risk factor (eg, hypertension, hyperlipidemia), and of these of 7 patients, 3 had less than 50% stenosis on coronary angiography (CAG). The other 4 patients did not undergo CAG. The mean and SD of the ejection fraction by ultrasonic cardiography, peak oxygen consumption (VO2) and rehabilitation period are shown in Table 1.

Method of Cardiac Sports Rehabilitation

The method of cardiac sports rehabilitation used in the present study followed that of Nohara et al and has been undertaken in Kyoto University since 1982, and Takeda General Hospital since 1988. Exercise tolerance was evaluated by a treadmill test according to the Bruce protocol and by a daily jog-walk program, consisting of 10 graded levels, which was used to evaluate the improvement in cardiac rehabilitation. Several kinds of sports were included in this program, such as jogging, walking, free gymnastics, stretching exercises, ping-pong, badminton, mini-tennis, volleyball, outings in the field. Nohara et al have already reported that sports therapy is generally effective and safe with few observable complications.

In addition, the important characteristics of this program for patients with CHD were an enjoyable sports program, and thus good compliance with continuing the exercise program.

Table 1 Clinical Data of the 37 Patients

<table>
<thead>
<tr>
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<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>66.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Peak VO2 (ml kg⁻¹ min⁻¹)</td>
<td>19.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Rehabilitation period (years)</td>
<td>5.9</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Measurement of Immune Function

Natural killer (NK) cell activity was determined by europium (Eu)-diethylenetriamine pentaacetic acid (DTPA) release assay. Conventionally, the activity of NK cells and lymphokine-activated killer (LAK) cells has been determined by the $^{51}$Cr-release assay. In that method, target cells are labeled with radioactive $^{51}$Cr and are destroyed by NK or LAK cells, with the released $^{51}$Cr radioactivity being determined. However, a method using a radioactive material has limitations, such as the necessity for special facilities. In addition, there is concern about the disposal of radioactive waste, and exposure to $^{51}$Cr, which has a short half-life and emits high-energy radiation, is a problem. The Eu-DTPA release assay, based on measurement of time-resolved fluorescence, can overcome all these problems and allow measurement of the activity of NK and LAK.

Fig 1. Correlation between the score on the extraversion scale in the Maudsley Personality Inventory and NK activity, which was assessed with the Eu-DTPA release assay using the human erythroleukemic cell line K562 as target. A significant positive correlation was observed in (♀) patients with coronary heart disease (n=37; r=0.50).

Fig 2. Correlation between the score on the neuroticism scale in the Maudsley Personality Inventory and NK activity, which was assessed with the Eu-DTPA release assay using the human erythroleukemic cell line K562 as target. A significant negative correlation was observed in (♂) patients with coronary heart disease (n=37; r=-0.39).

Fig 3. Correlation between the score on the playful humor scale and NK activity, which was assessed with the Eu-DTPA release assay using the human erythroleukemic cell line K562 as target. A significant positive correlation was observed in (♀) patients with coronary heart disease (n=37; r=0.43).
cells with a sensitivity comparable to or higher than that of the conventional $^{51}$Cr-release assay. Target cells are labeled with non-radioactive Eu-DTPA and are destroyed by NK or LAK cells, with the released Eu-DTPA being measured by time-resolved fluorescence.

**Psychological Tests**

The scales used in the present study were the Moudsley Personality Inventory (MPI), Humor Scale, Zung’s Self-rating Depression Scale (SDS), McNair’s Profile of Mood States (POMS), and the anger scale of the Mine’s Japanese Version of Spielberger’s State-Trait Anger eXpression Inventory (STAXI).

The STAXI consists of 44 items, including 6 scales (state anger, trait anger, anger-in, anger-out anger-control, anger-expression) and 2 subscales (angry temperament,
Anger-in Scale An 8-item anger expression scale that measures the frequency with which angry feelings are held in or suppressed. The person with high anger-in scores frequently experiences intense anger feelings, but tends to suppress these feelings rather than express them in either physical or verbal behavior. It should be noted, however, that the same person who has a high score in anger-in might also have a high anger-out score, in which case anger is expressed in some situations and suppressed in others.

Anger-out Scale An 8-item anger expression scale that measures how often an individual expresses anger toward other people or objects in the environment. The person with a high anger-out score frequently experiences anger that is
expressed in aggressive behavior directed towards other persons or objects in the environment. Anger-out may be expressed in physical acts such as assaulting other persons or slamming doors, or it may be expressed verbally in the form of criticism, sarcasm, insults, threats, and the extreme use of profanity.

Anger-control Scale An 8-item anger expression scale that measures the frequency with which an individual attempts to control the expression of anger. The person with a high score of the anger-control scale tends to invest a great deal of energy in monitoring and preventing the experience and expression of anger. Although it is certainly desirable to control anger, the over-control of anger may result in passivity, withdrawal and depression in those with a high anger-control score but who also have a high trait-anger score and low anger-out score.

The Type A scale used 'the questionnaire for detection of psychosocial factors affecting cardiovascular health management', which is described by Hayashi et al. This questionnaire consists of a total of 26 items, including sex, age, weight ratio, and 23 other questions. A quantification method of the second type was used to examine whether the presence of cardiovascular disease, hypertension or hyperlipidemia was predictive of the 26 items. The quantification method gave numerical values (category scores) to the categories (nominal scales) of each item. Furthermore, the prediction scores calculated from the results of the quantification method of the second type, and the incidence of diseases, were obtained by the total scores for each disease.

Procedure Medical examinations, such as blood collection for measurement of immune function or exercise tolerance tests were performed in all the patients, from whom informed consent had been obtained. In addition, the various psychological scales were assessed.

Blood collection for immune function was performed at rest, before the Bruce treadmill test, in 7 patients per day, and 1 patient per hour from 09.00h to 16.00h. Data were collected from 8 March to 17 March, 1998.

Results

The Pearson’s product-moment correlation coefficient between NK cell activity and each psychological scale was obtained. For the MPI, NK cell activity had a significant positive correlation with the extraversion scale (Fig 1) and a significant negative correlation with the neuroticism scale (Fig 2).

In addition, the mean and SD of the Lie (L) scale for MPI were 15.23 and 3.25. The observations of low reliability over 21 points for L scale had been omitted previously.

For the humor scale, although no significant correlation was observed in the aggressive humor scale, NK cell activity had a significant positive correlation with the playful humor scale (Fig 3). For the POMS, NK cell activity had a tendency to correlate positively with vigor-activity (Fig 4) and negatively with tension-anxiety (Fig 5) and had a significant negative correlation with depression-dejection (Fig 6) as well as with fatigue-inertia (Fig 7). NK cell activity had a significant negative correlation with the SDS (Fig 8). For the Type A scale, NK cell activity had a significant negative correlation only with the hypertension scale (Fig 9). NK cell activity was not correlated with any subscale (anger-in, anger-out, anger-control) of the STAXI anger expression scale.

Discussion

The extraversion scale is used to measure the tendency to be sociable, mischievous, free of care and optimistic and readily express anger. The neuroticism scale is used to measure the tendency to show marked emotional reactions to various stimuli, be unstable in terms of autonomic responses, and be excited. The humor scale is used to measure the tendency to like and express humor. Therefore, the positive correlation of NK cell activity with the extraversion scale as well as the humor scale and its negative correlation with the neuroticism scale indicate an association between NK cell activity and a positive-feeling tendency. On the other hand, the negative correlation of NK cell activity with the depression scale, neuroticism scale, and each POMS subscale suggests that decreased or excessive expression of feelings inhibits NK cell activity. Thus, high NK activity appears to be associated with optimal expression of feelings. NK activity was not associated with the scales for prediction of cardiovascular diseases from the behavioral aspect; no association was observed between psychological factors related to the tendency of a Type A behavior pattern and immune function. NK activity was not associated with the anger scale, which recently has been considered to be more closely associated than the Type A behavior pattern with coronary heart disease. Previous studies have shown that negative feelings such as anger and hostility inhibit immune responses; inhibition of negative feelings causes persistent chronic autonomic responses and the resulting increase in corticosteroids inhibits immune responses. Therefore, we speculated that the anger-in or anger-control tendency would be associated with immune responses, but in the present study no association was observed between psychological tendencies related to the development of cardiovascular diseases and immune responses.

Sakakibara, who observed the association between cancer cell growth and stress in rats, suggested an association between psychological factors and immune function. Henry et al found rapid cancer cell growth in mice kept in isolation and Newberry et al reported on the effects of electric shock on tumor formation in rats. Riley et al observed the influence of stress on tumor formation and suggested the importance of adrenocortical hormones as its mechanism. In those studies, which used physical stimuli such as strong light stimulation or electric shock, immune function was not directly measured. Due to subsequent advances in immunology, direct measurement of lymphocytes, such as T and B cells, has become possible. Initially, lymphocyte activity was measured after stimulation using concanavalin A (Con A) as a mitogen. Using that method, Bartrop et al found that the lymphocyte response to Con A was reduced during the 2 months after the death of a spouse compared with the response of a control group. Similarly, Schleifer et al evaluated lymphocyte reactivity to a mitogen in males who lost their spouse and observed a significant decrease before and after the spouse’s death compared with the control group. As lymphocytes associated with inhibition of cancer cells, NK cells began to attract attention. Greene et al reported significantly decreased NK cell activity in the presence of marked psychological distress due to marked changes in life. Other psychological states also
have been reported to affect immune responses. Stain et al found decreased lymphocyte reactivity to mitogens in patients with depression and an association between the degree of the decrease in lymphocyte reactivity and the severity of depression.10 Another study showed decreased function of the immune system and decreased helper T cells in patients with psychiatric diseases.11 Thus, these studies, which directly measured immune responses to psychological stress, have demonstrated the association between decreased immune response and conditions such as depression and grief. Based on these results, studies on stress states and personality in cancer patients have been carried out,12 which concluded that psychological or behavioral stress is not directly related to the development of tumors, but decreased immune function affected tumor growth.3

The association between exercise or training and immune function has also been studied. Stain et al were the first to report changes in the B/T lymphocyte ratio after exercise.14 In recent years, changes in the T lymphocyte subgroups after exercise or training have been evaluated. It was reported that helper T cells decrease and suppressor T cells increase immediately after exercise irrespective of its intensity, but both types of T cells return to the pre-exercise level 2 h after discontinuation of exercise.15 Hashimoto et al evaluated immune responses in rats in a 7-week training group, an acute exercise group, and a control group and found a decrease in lymphocytes in the acute exercise group and enhanced granulocyte phagocytosis in the training group.16 Reactivity to ConA was reported to decrease after acute exercise irrespective of its intensity.17 However, the results from previous studies on the effects of long-term training (4 weeks–some months) on lymphocyte reactivity have been inconsistent; some studies showed an increase,18 but others showed a decrease19 or no change.20

Study Limitation

In the present study, the association between psychological tendencies and immune responses was evaluated in patients with cardiovascular diseases under exercise therapy. However, the data obtained in this study lacks comparison with a control group. Therefore, whether the results obtained in are characteristic of patients with cardiovascular diseases or due to exercise therapy can not be determined at present. We intend performing further studies to collect serial data in healthy normal subjects and patients with cardiovascular diseases who are not receiving exercise therapy.

References


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