Cardiac Neurosis: Exercise Tolerance and the Role of Sympathetic Activity

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To evaluate the cardiovascular and plasma catecholamine responses to dynamic exercise in patients with cardiac neurosis (CN), treadmill testing was performed. Thirty-four patients with CN were chosen for this study based on exercise tolerance and the results were compared with those in 31 patients with organic heart disease and 12 normal subjects. Patients with CN showed an augmentation of cardiovascular and plasma catecholamine responses. The augmentation of the norepinephrine response in patients with CN was not as remarkable as that in patients with organic heart disease. On the other hand, the augmentation of the epinephrine response was greater in patients with CN than in those with organic heart disease. Administration of metoprolol (40 mg/day) for two weeks improved exercise tolerance in patients with CN. We suggest that anxiety augments both sympatho-neural and sympatho-adrenal activity and that it is the symptoms induced by the augmented cardiovascular response which reduce exercise tolerance in patients with CN.

Key words: Irritable heart syndrome, Hyperkinetic heart syndrome, Neurocirculatory asthenia, Treadmill exercise testing, Plasma catecholamine concentrations, Beta blocker

Cardiac neurosis (CN) is a psychophysiological syndrome characterized by cardiovascular and nervous symptoms in the absence of underlying organic disorders. This syndrome is regarded to be similar to irritable heart syndrome (1), soldier's heart, effort syndrome, hyperkinetic heart syndrome (2), hyperdynamic beta-adrenergic circulatory state (3), and neurocirculatory asthenia. Dyspnea, palpitation and nervousness are common symptoms both at rest and during effort. This condition is assumed to be a hyperkinetic cardiovascular state based on anxiety. Sympathetic activity has an important role in cardiovascular response to a variety of stress types. Previous studies (4–6) showed an increase in plasma catecholamine concentrations in patients with panic and anxiety disorders. However, few reports have been published on the plasma catecholamine response to dynamic exercise in patients with CN and in these reports the results do not agree (7–9). The purpose of this study was to investigate whether or not the characteristic response of plasma catecholamines to dynamic exercise occurs in patients with CN. Therefore, the cardiovascular and plasma catecholamine responses during treadmill exercise testing were evaluated in patients with CN and the results were compared with those in patients with organic heart disease and in normal subjects. Additionally, the effects of blockade of beta-adrenergic receptors on exercise tolerance was evaluated.

METHODS

Subjects
We studied 34 patients (11 men, 23 women; mean age 48 ± 13 years) with symptoms characteristic of CN (dyspnea, palpitation, nervousness and anxiety), 31 patients (11 men, 20 women; mean age 53 ± 10 years) with organic heart disease, and 12 normal subjects (8 men, 4 women; mean age 42 ± 14 years).
The diagnosis of CN was made based on physical and laboratory examinations (chest roentgenography, electrocardiography, 24-h ambulatory electrocardiographic recording, echocardiography, spirometry, etc.) and explanatory cardiovascular, respiratory, and endocrine diseases were excluded.

The 31 patients with organic heart disease consisted of 4 patients with old myocardial infarction without angina pectoris, 1 patient with dilated cardiomyopathy, 8 patients with aortic valvular disease, 14 patients with mitral valvular disease, and 4 patients with atrial septal defect. Twelve patients had atrial fibrillation. Fourteen patients were receiving long-term digitalis and diuretic therapy, and 9 patients were receiving long-term vasodilator therapy. Vasodilators were withdrawn for 48 h prior to exercise testing.

**Treadmill exercise testing**

A 19-gauge indwelling catheter was placed in the antecubital vein of the right arm and a small amount of physiological saline was continuously infused. Subjects remained in the supine position for 15 min. Blood (3 ml) was drawn for the measurement of plasma catecholamine concentration. Blood pressure was measured with an automatic sphygmomanometer (Nippon Colin, STBP-680) on the left arm. Multistage treadmill exercise testing was performed on a computerized system (Marquette, CASE 2) according to the modified Bruce protocol (10) in which the load level was increased every 3 min and a stage of 3.8 mph and 14% was added. Electrocardiogram recording and measurement of blood pressure were performed every min during exercise. End points were defined as the occurrence of moderate dyspnea or palpitation in patients and the achievement of 85% of age-predicted maximal heart rate in normal subjects. Blood samples were obtained during the last min of each exercise stage in normal subjects and immediately after exercise in all patients and normal subjects. Patients without moderate symptom on achievement of 85% of age-predicted maximal heart rate were excluded. Exercise time in treadmill testing was regarded as the index of exercise tolerance. Poor tolerance was defined as the exercise time from 3 to 7 min, when exercise tolerance was a work load of the first or second exercise stage. Fair tolerance was defined as the exercise time from 8 to 10 min, when exercise tolerance was a work load of the third exercise stage. And good tolerance was defined as the exercise time of 11 min or more, when exercise tolerance was a work load of the fourth exercise stage or more.

**Measurement of plasma catecholamine concentrations**

Blood samples were kept in ice water. After centrifugation, plasma samples were kept frozen at -40°C. Plasma norepinephrine and epinephrine concentrations were measured by the THI (tri-hydroxyindole) method with a high-performance liquidchromatograph.

**Evaluation of effects of metoprolol**

Effects of metoprolol on exercise tolerance and cardiovascular response to exercise were evaluated in 8 patients with CN. After consent was obtained, the daily dosage of metoprolol, 40 mg, was administered in two portions. The concomitant use of anti-anxiety drugs was avoided. Two weeks after administration, treadmill exercise testing was repeated. Exercise after administration was terminated by the appearance of a symptom equivalent to that in the test before administration.

**Statistical analysis**

Data are represented as mean ± SD in the text and mean±SEM in the figures. Data were analyzed using the t-test. p values of less than 0.05 were considered significant.

**RESULTS**

**Exercise tolerance (Table 1)**

Of 34 patients with CN, 13 had poor tolerance, 10 had fair tolerance, and 11 had good tolerance. Of 31 patients with organic heart disease, 20 had poor tolerance, and 11 had fair tolerance. All 12 normal subjects had good tolerance. Then heart rate, systolic blood pressure, plasma norepinephrine and epinephrine concentrations at rest and at the peak exercise in both patient groups with poor tolerance were compared with those at rest and at the end of the second exercise stage in normal subjects, respectively. The results at rest and at the peak exercise in both patient groups with fair tolerance were compared with those at rest and at the end of the third exercise stage in normal subjects, respectively. And the results at rest and at the peak exercise in the CN patient group with good tolerance...
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Table 1. Patient grouping based on exercise tolerance.

<table>
<thead>
<tr>
<th>Exercise tolerance</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
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<tbody>
<tr>
<td>n ET</td>
<td></td>
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<tr>
<td>Cardiac neurosis</td>
<td>13</td>
<td>10</td>
<td>11</td>
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<tr>
<td>4.8±1.4*</td>
<td>9.4±1.0</td>
<td>13.9±1.3</td>
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<tr>
<td>Organic heart disease</td>
<td>20</td>
<td>11</td>
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<tr>
<td>5.1±1.4</td>
<td>9.0±0.9</td>
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<tr>
<td>Normal</td>
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<td>14.3±0.9</td>
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n, number of patients; ET, exercise time (min)
*Values are mean±SD.

were compared with those at rest and at the peak exercise in normal subjects, respectively.

Heart rate (Fig. 1)

Heart rate (HR) at rest was significantly higher in the poor tolerance CN group than in normal subjects. HR at the peak exercise in both patient groups with poor tolerance (CN, 140±16; organic heart disease, 134±19 beats/min) was significantly higher than that at the end of the second exercise stage in normal subjects (102±13 beats/min). HR at the peak exercise in both patient groups with fair tolerance (CN, 145±13; organic heart disease, 135±20 beats/min) was significantly higher than that at the end of the third exercise stage in normal subjects (118±11 beats/min). And there was no significant difference in HR at the peak exercise between the good tolerance CN group (147±15 beats/min) and normal subjects (148±15 beats/min).

Systolic blood pressure (Fig. 2)

The systolic blood pressure (SBP) of patients with CN and that of normal subjects was compared as the SBP response is influenced by organic heart disease. SBP at rest and at the peak exercise in the poor tolerance CN group (exercise, 167±25 mmHg) was significantly higher than that at rest and at the end of the second exercise stage in normal subjects (exercise, 134±17 mmHg), respectively. SBP at the peak exercise in the fair tolerance CN group (170±35 mmHg) tended to be higher than that at the end of the third exercise stage in normal subjects (145±17 mmHg) (p<0.1). And there was no significant difference in SBP at the peak exercise between

Fig. 1. Heart rate (HR) response to multistage treadmill exercise in patients with cardiac neurosis (CN), those with organic heart disease (H), and normal subjects (N). Patients were grouped based on exercise tolerance (poor, fair or good). HR at the peak exercise in patient groups was compared with that at the equivalent level of exercise (at the end of the second or third exercise stage or at the peak exercise) in normal subjects. *p<0.05.

Fig. 2. Systolic blood pressure (SBP) response to multistage treadmill exercise in patients with cardiac neurosis (CN) and normal subjects (N). Patients were grouped based on exercise tolerance. SBP at the peak exercise in patient groups was compared with that at the equivalent level of exercise in normal subjects. *p<0.05.
the good tolerance CN group (171 ± 16 mmHg) and normal subjects (162 ± 14 mmHg).

Plasma norepinephrine concentration (Fig. 3)

There was no significant difference in plasma norepinephrine (NE) concentration at rest between the poor tolerance CN group (152 ± 52 pg/ml) and normal subjects (123 ± 37 pg/ml). Plasma NE concentration at rest was significantly higher in the poor tolerance organic heart disease group (223 ± 115 pg/ml) than in either the poor tolerance CN group or normal subjects. Plasma NE concentration at the peak exercise in both patient groups with poor tolerance (CN, 675 ± 357; organic heart disease, 954 ± 488 pg/ml) was significantly higher than that at the end of the second exercise stage in normal subjects (265 ± 79 pg/ml). There was no significant difference in plasma NE concentration at the peak exercise between both patient groups with poor tolerance. There were no significant differences in plasma NE concentration at rest among patient groups with fair tolerance (CN, 146 ± 51; organic heart disease, 180 ± 85 pg/ml) and normal subjects. Plasma NE concentration at the peak exercise in the fair tolerance CN group (676 ± 279 pg/ml) was significantly higher than that at the end of the third exercise stage in normal subjects (305 ± 90 pg/ml). Plasma NE concentration at the peak exercise in the good tolerance CN group (724 ± 321 pg/ml) was significantly higher than that at the equivalent level of exercise in the fair tolerance CN group and in normal subjects. And plasma NE concentration at the peak exercise was significantly higher in the good tolerance CN group (724 ± 321 pg/ml) than in normal subjects (461 ± 169 pg/ml), while there was no significant difference in plasma NE concentration at rest between these two groups (CN, 130 ± 28 pg/ml).

Plasma epinephrine concentration (Fig. 4)

Plasma epinephrine (E) concentration at rest was significantly higher in the poor tolerance CN group (45 ± 36 pg/ml) than in normal subjects (22 ± 11 pg/ml). Plasma E concentration at rest in the poor tolerance organic heart disease group (25 ± 24 pg/ml) was not significantly different from that at rest in the poor tolerance CN group or in normal subjects. Plasma E concentration at the peak exercise in the poor tolerance CN group (108 ± 66 pg/ml) was significantly higher than that at the peak exercise in the poor tolerance organic heart disease group (48 ± 25 pg/ml) and at the end of the second exercise stage in normal subjects (28 ± 19 pg/ml). Plasma E concentration at the peak exercise in the poor tolerance organic heart disease group was not significantly different from that at the end of the
second exercise stage in normal subjects. There were no significant differences in plasma E concentration at rest among patient groups with fair tolerance (CN, 19 ± 12; organic heart disease, 20 ± 10 pg/ml) and normal subjects. Plasma E concentration at the peak exercise in the fair tolerance CN group (75 ± 44 pg/ml) tended to be higher than that at the end of the third exercise stage in normal subjects (44 ± 23 pg/ml) (p <0.1). Plasma E concentration at the peak exercise in the fair tolerance organic heart disease group (59 ± 46 pg/ml) was not significantly different from that at the peak exercise in the fair tolerance CN group and at the end of the third exercise stage in normal subjects. There was no significant difference in plasma E concentration either at rest or at the peak exercise between the good tolerance CN group (rest, 22 ± 12; exercise, 65 ± 33 pg/ml) and normal subjects (exercise, 53 ± 24 pg/ml).

Changes in plasma norepinephrine concentration (Fig. 5)
The change in plasma NE concentration (ΔNE) was measured by comparing plasma NE concentration at rest with the value at the peak exercise in patients with CN and those with organic heart disease, and by comparing plasma NE concentration at rest with the value at the end of the second or third exercise stage, or at the peak exercise in normal subjects. There was no significant difference in ΔNE between the patient groups with poor tolerance (CN, 522 ± 324; organic heart disease, 724 ± 447 pg/ml). ΔNE in both patient groups with poor tolerance was significantly higher than that at the end of the second exercise stage in normal subjects (143 ± 53 pg/ml). ΔNE in the fair tolerance CN group (537 ± 236 pg/ml) was significantly higher than that at the end of the third exercise stage in normal subjects (188 ± 71 pg/ml). ΔNE in the fair tolerance organic heart disease group (955 ± 479 pg/ml) was significantly higher than that in the fair tolerance CN group and that at the end of the third exercise stage in normal subjects. ΔNE in the good tolerance CN group (594 ± 329 pg/ml) was not significantly different from that at the peak exercise in normal subjects (378 ± 150 pg/ml).

Changes in plasma epinephrine concentration (Fig. 6)
The change in plasma E concentration (ΔE) was measured in the same manner as ΔNE. ΔE in the poor tolerance CN group (64 ± 52 pg/ml) was significantly higher than that in the poor tolerance organic heart disease group (25 ± 19 pg/ml) and that at the end of the second exercise stage in normal subjects (7 ± 13 pg/ml). ΔE in the poor tolerance organic heart disease group was significantly higher than that at the end of the second exercise stage in normal subjects. There was no significant difference in ΔE between the patient groups with fair
tolerance (CN, 55 ± 38; organic heart disease, 44 ± 39 pg/ml); J E in these two groups was significantly higher than that at the end of the third exercise stage in normal subjects (21 ± 21 pg/ml). J E in the good tolerance CN group (43 ± 31 pg/ml) was not significantly different from that at the peak exercise in normal subjects (42 ± 31 pg/ml).

Effects of metoprolol (Fig. 7)

After administration of metoprolol, the exercise time was significantly prolonged (from 7.5 ± 4.6 to 10.8 ± 3.4 min). HR at rest significantly decreased from 77 ± 11 to 62 ± 9 beats/min. HR both at the time equal to the peak exercise time before administration (102 ± 12 beats/min) and at the peak exercise (124 ± 16 beats/min) was significantly lower than the value at the peak exercise before administration (145 ± 13 beats/min). SBP at rest remained unchanged (135 ± 18 vs 130 ± 30 mmHg). SBP at the time equal to the peak exercise time before administration (156 ± 16 mmHg) was significantly lower than the value at the peak exercise before administration (183 ± 31 mmHg). SBP at the peak exercise tended to decrease (from 183 ± 31 to 174 ± 29 mmHg, p<0.1). No obvious side effects were observed.

DISCUSSION

In recent years the psychophysiological syndrome represented by CN has been considered to be a clinical entity based on anxiety. CN is characterized by symptoms suggesting sympathetic hyperactivity. Plasma catecholamine concentrations are considered to be an index of sympathetic activity. Generally, emotional stress induces mainly an increase in epinephrine from adrenal medullae. On the other hand, dynamic exercise stress induces primarily an increase in norepinephrine from postganglionic sympathetic nerves. Several reports showed an increase in plasma norepinephrine and/or epinephrine concentrations at rest in patients with anxiety disorders (4–6). However, only a few reports on the relation between the reduction of work capacity and the response of sympathetic activity to dynamic exercise stress in patients with CN have been published and the published results are not in agreement (7–9). And there is no report on the comparison of the response of sympathetic activity to exercise between patients with CN and those with organic heart disease. Francis et al (11) reported that the plasma norepinephrine concentration is elevated at rest and is more markedly increased at lower levels of dynamic exercise in patients with congestive heart failure than in normal subjects. This increase is attributed to the reflex stimulation of the sympathetic nervous system which may support cardiac function. On the other hand, the plasma epinephrine concentration was similar between these two groups at rest, and showed changes during dynamic exercise somewhat similar to those of plasma norepinephrine concentration. However the difference between these two groups at lower levels of dynamic exercise was not as remarkable as plasma norepinephrine concentration. This finding indicates that adrenal medullae are not major sources of plasma catecholamines during dynamic exercise. The progression of anaerobic metabolism in peripheral organs during exercise is assumed to be a stimulus in the activation of the sympathetic nervous system (12).

In this study we confirmed the reduction of exercise tolerance in patients with CN. Then we divided patients with CN and those with organic heart disease into groups based on exercise tolerance, and compared the cardiovascular and plasma...
catecholamine responses to exercise among patient groups and normal subjects. Patients with CN, those with a reduction in exercise tolerance in particular, showed a hyperkinetic cardiovascular state and sympathetic hyperactivity. The norepinephrine response was augmented in patients with CN, however this augmentation was not as remarkable as that in patients with organic heart disease, while the heart rate response was similar between these two groups. On the other hand, the augmentation of the epinephrine response was greater in patients with CN than in those with organic heart disease. These findings suggest that anxiety augments sympathetic and sympatho-adrenal activity.

Since Granville-Grossman and Turner (13) reported in 1966 the efficacy of beta blockers on anxiety, many similar reports have been published. And the mechanism of the anti-anxiety action of the drug is assumed to be a feedback of the reduction of peripheral symptoms (14). In this study, inspite of the small dose, metoprolol significantly reduced cardiovascular hyperactivity and augmented exercise tolerance in patients with CN. This finding suggests that it is the symptoms induced by cardiovascular hyperactivity which account for the reduction in exercise tolerance (15).

Thus, we conclude that the hyperactivity of the sympathetic nervous center is related to the augmentation of the cardiovascular and plasma catecholamine responses to exercise in patients with CN and that beta blocker therapy is useful.

REFERENCES