Exercise-Induced Changes in Plasma Atrial Natriuretic Peptide and Brain Natriuretic Peptide Concentrations in Healthy Subjects With Chronic Sleep Deprivation

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Recent observations have shown that plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) correlate with cardiac function or prognosis in heart failure patients. However, relatively little is known about changes in their plasma concentration during commonly occurring physiological states such as fatigue. Therefore, this study was designed to examine the physiological changes of plasma ANP and BNP concentrations using a chronic sleep-deprivation model. Bicycle ergometer cardiopulmonary exercise tests were performed in 10 healthy volunteers (mean age: 22.7 years). Blood samples for measuring ANP and BNP were drawn during the resting state and immediately after each exercise test. Cardiac output (CO) was measured during the exercise test by the impedance method. The study conditions were designed as follows: (A) a day following a period of normal sleep (control state) and (B) a day preceded by 1 month during which sleep lasted <60% of normal (chronic sleep-deprived state). Results were as follows. (1) Peak oxygen uptake and peak CO decreased during the sleep-deprived state compared with the control state. (2) There was no difference between peak heart rates measured during exercise under the 2 conditions. (3) Plasma ANP concentration during exercise increased significantly during the control state, whereas only a tendency toward increase was observed during the sleep-deprived state. (4) Plasma BNP concentration during exercise tended to increase in the control state compared with the resting state, whereas there was no difference in plasma BNP between after exercise and resting state in the sleep-deprived state. These results indicate that changes of ANP or BNP induced by exercise tended to be decreased by chronic sleep deprivation. (Jpn Circ J 1999; 63: 447–452)

Key Words: Atrial natriuretic peptide;Brain natriuretic peptide;Exercise tolerance;Sleep deprivation

The secretion of atrial natriuretic peptide (ANP) is stimulated by tachycardia and atrial volume expansion associated with increased atrial pressure and stretch. It is widely accepted that the plasma ANP level increases along with the severity of congestive heart failure (CHF) and its level is related to prognosis in patients with CHF. Previous clinical studies have identified ANP secretion increases in response to exercise in healthy subjects as well as in cardiac patients.

Plasma brain natriuretic peptide (BNP) is elevated in patients with essential hypertension, the acute stage of myocardial infarction or with CHF. Its plasma level may reflect the degree of left ventricular dysfunction. A high concentration of plasma BNP is also considered to indicate possible left ventricular dysfunction or poor prognosis in patients with CHF.

Our current study revealed that exercise increased not only the plasma ANP concentration, but also that of BNP in healthy subjects and in patients with CHF. These combined findings have demonstrated that high plasma ANP and BNP concentrations may reflect the degree of left ventricular dysfunction or a poor prognosis in patients with CHF. In addition, it has been postulated that the magnitude of exercise-induced ANP or BNP secretion may be influenced by the sympathetic nervous system. In regard to these reports, the measurement of circulating ANP and BNP may be a sensitive measure for detecting left ventricular dysfunction or a poor prognosis in cardiac patients. However, little is known about changes in plasma ANP and BNP concentrations during commonly occurring physiological states such as fatigue. The aim of the present study was to clarify whether plasma ANP and BNP concentrations are affected by chronic fatigue, using a model of chronic sleep deprivation. In addition, plasma norepinephrine (NE) concentration, exercise tolerance, and cardiac output (CO) during exercise were measured and compared with changes in ANP and BNP concentrations.

Methods

The subjects of this study consisted of 10 healthy male volunteers (college students whose mean age was 22.8±1.2 years). All subjects had no past history of serious disease. Their present health status was checked by routine physical examination, chest X-ray, resting ECG, and routine labora-
Table 1 Serial Changes in Exercise Tolerance

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sleep deprived</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT (ml min⁻¹ kg⁻¹)</td>
<td>19.3±1.6</td>
<td>16.9±1.3</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>AT time (s)</td>
<td>241.4±33.3</td>
<td>193.0±29.8</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Peak VO₂ (ml min⁻¹ kg⁻¹)</td>
<td>43.4±5.6</td>
<td>41.5±5.1</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Peak exercise time (s)</td>
<td>708.2±63.6</td>
<td>689.4±72.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR, heart rate; BP, blood pressure; AT, anaerobic threshold; CO, cardiac output; Peak VO₂, peak oxygen uptake.

Table 2 Serial Changes in Heart Rate (HR) and Blood Pressure (BP) During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sleep deprived</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR at rest (beats/min)</td>
<td>80.1±10.9</td>
<td>83.4±7.1</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Systolic BP at rest (mmHg)</td>
<td>121.6±8.7</td>
<td>122.6±11.8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP at rest (mmHg)</td>
<td>80.7±6.7</td>
<td>88.8±13.5</td>
<td>NS</td>
</tr>
<tr>
<td>HR at AT (beats/min)</td>
<td>121.0±8.7</td>
<td>119.4±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP at AT (mmHg)</td>
<td>145.8±15.3</td>
<td>158.2±15.0</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP at AT (mmHg)</td>
<td>85.1±11.0</td>
<td>90.6±14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>189.4±8.8</td>
<td>192.9±7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Peak systolic BP (mmHg)</td>
<td>203.1±18.7</td>
<td>206.6±22.0</td>
<td>NS</td>
</tr>
<tr>
<td>Peak diastolic BP (mmHg)</td>
<td>97.6±9.0</td>
<td>98.1±8.8</td>
<td>NS</td>
</tr>
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</table>

AT, anaerobic threshold.

Results

Temporal Changes in Exercise Tolerance (Table 1)

For all subjects, the endpoint of the exercise test was leg fatigue or shortness of breath. No subjects experienced ischemic ST change or severe arrhythmia. The mean values of AT, AT time, and peak VO₂ in the chronically sleep-deprived state were significantly lower than those in the control state. There was no significant difference in peak exercise time between the control and chronically sleep-deprived states.

Measurement of Plasma ANP, BNP, and NE Concentrations

For the measurement of plasma ANP and BNP concentrations, 5 ml of venous blood was drawn from the cubital vein and immediately aspirated into a polypropylene tube containing 4.5 mg of EDTA-2Na and 150 μl of tradirol. The sampled blood was immediately ice-cooled and centrifuged at 3000 rpm for 10 min at 4°C, thereby separating the plasma, which was maintained in frozen storage at –70°C until needed for analysis. Plasma ANP concentration was measured by a radio-immunodassay (Shionoria BNP, Osaka, Japan) using 2 monoclonal antibodies.

The plasma concentration of NE was analyzed with high-performance liquid chromatography using blood samples that had been collected in polypropylene tubes containing EDTA, centrifuged at 3000 rpm for 10 min and the plasma extracted.

All data are expressed as the mean value±SD. Differences between the control state and sleep-deprived state or between the resting value and the value after exercise were evaluated by Fisher’s PLSD after an initial evaluation by one-way analysis of variance. A value of p<0.05 was considered significant, and a value of p<0.1 was considered as showing a tendency toward significance.
Fig 1. Serial changes in peak cardiac output and exercise-induced changes in cardiac output. Peak CO and exercise-induced change in CO were lower when subjects were in the chronically sleep deprived state than when they were in the control state. CO, cardiac output; ΔCO, exercise-induced change in cardiac output.

Fig 2. Exercise-induced changes in plasma ANP concentration. ANP concentration increased significantly after exercise testing in the control state, while only a tendency toward increase was observed in the chronically sleep deprived state. ANP, atrial natriuretic peptide.

Fig 3. Exercise-induced changes in plasma BNP concentration. BNP concentration tended to increase after exercise testing in the control state, whereas there was no difference between resting state and peak exercise in the chronically sleep deprived state. BNP, brain natriuretic peptide.
The mean values of resting HR during the control state and the chronically sleep-deprived state were 80.1±10.9 beats/min and 83.4±7.1 beats/min, respectively, with the value during the chronic sleep deprivation being significantly higher (p<0.05). Comparison of both states revealed no significant difference in peak HR; the mean peak HR was 189.4±8.8 beats/min (control state) and 192.9±7.0 beats/min (chronically sleep deprived state). Comparison between both states revealed no significant difference in peak HR.

There was no significant difference in blood pressure at rest, at AT, or at peak exercise between the control state and the chronic sleep-deprived state.

Temporal Changes in CO

The mean values of CO at rest were 5.8±1.2 L/min in the control state and 5.9±1.1 L/min in the chronic sleep-deprived state. Fig 1 shows the peak CO and ∆CO during exercise testing in 8 subjects who were evaluated completely. The mean CO level at peak exercise was significantly lower (p<0.05) during chronic sleep deprivation than during normal sleep (23.9±4.2 and 26.4±3.4 L/min, respectively). The mean value of ∆CO also was significantly lower (p<0.05) during chronic sleep deprivation than during normal sleep (17.9±3.5 and 20.6±2.8 L/min, respectively).

Temporal Changes in ANP and BNP Concentration During Exercise

ANP concentration increased significantly after exercise testing in the control state (from 8.3±4.4 to 15.6±11.0 pg/ml), whereas only a tendency toward increase was found in chronic sleep deprivation (from 5.2±0.7 to 9.2±5.1 pg/ml) (Fig 2). The BNP concentration tended to increase after exercise testing in the control state (from 5.5±2.7 to 9.1±6.2 pg/ml), whereas there was no significant difference in BNP between the resting state and peak exercise during the chronic sleep-deprived state (4.0±0.0 vs 4.3±0.9 pg/ml) (Fig 3).

In comparing plasma ANP and BNP concentration between the control and sleep-deprived states, plasma ANP concentration immediately after exercise in the sleep-deprived state tended to be low compared with the control state (p<0.1). There was no significant difference between the 2 conditions with respect to plasma ANP at the resting state and plasma BNP concentration.

Resting NE concentrations in the control state and during the chronically sleep-deprived state were 250.2±64.2 pg/ml and 372.7±115.3 pg/ml (p<0.05), respectively. The corresponding NE concentrations at peak exercise were 3432.5±1538.3 pg/ml and 3842.3±1498.1 pg/ml (not significant).

Correlation Between ANP or BNP Concentration and NE, HR and CO (Fig 4)

Plasma ANP concentration at peak exercise showed a tendency toward a positive correlation with peak NE concentration (r=0.43, p<0.1). However, plasma ANP concentration at peak exercise had no correlation with peak HR, peak CO, or ∆CO. No correlation was observed between BNP concentration and peak NE concentration, peak HR, peak CO, or ∆CO.

Discussion

In previous studies, plasma ANP concentration correlated closely with pulmonary wedge pressure, HR, or plasma NE concentration and the plasma BNP level seemed to reflect the degree of left ventricular dysfunction. Clinical studies have documented plasma ANP and BNP concentration increases in response to exercise in healthy subjects as well as in hypertensive subjects and patients with CHF. High concentrations of these peptides are also considered to indicate left ventricular dysfunction or poor prognosis in patients with CHF. However, it is not clear whether these plasma concentrations are affected by changes in physiological conditions such as chronic sleep deprivation. In the present study, we compared plasma ANP and BNP responses to exercise in subjects during chronic sleep deprivation and during a normal control state.

Relationship Between Plasma ANP and BNP Concentrations and Cardiac Function

Matsumoto et al compared plasma levels of ANP and BNP at rest and during bicycle exercise in patients with dilated cardiomyopathy or mitral stenosis. In that study, the severity of heart failure in terms of symptoms and resting hemodynamics, such as atrial pressure, was similar in both groups; however, the patients with dilated cardiomyopathy had a higher left ventricular end-diastolic pressure and a lower left ventricular ejection fraction than those with mitral stenosis. The patients with dilated cardiomyopathy also had higher plasma BNP levels at rest and during exercise than the patients with mitral stenosis.
although there was no difference in their plasma ANP levels. The authors concluded that the increased secretion of BNP may originate from pressure and volume overload of the left ventricle or from ventricular stretch, which is one of the most important stimuli for the release of BNP. Yokoyama et al investigated changes in plasma BNP level during exercise and serial plasma BNP changes in patients during the recovery phase of myocardial infarction. Plasma BNP level increased significantly following exercise at both 1 and 3 months after infarction onset. Morita et al reported that BNP secretion from the left ventricle increased after the occurrence of myocardial infarction and that its plasma level could reflect the degree of left ventricular dysfunction by the negative correlation between the ejection fraction and BNP concentration and by the positive correlation between left ventricular end-diastolic pressure and BNP secretion. Our present study revealed that exercise-induced plasma levels of ANP and BNP associated with chronic sleep deprivation were lower than those associated with normal sleep, although there was no difference with regard to peak HR or peak exercise time. Peak CO during exercise testing following chronic sleep deprivation was significantly lower than its level following normal sleep, whereas there was no difference with regard to peak blood pressure between the control and chronically sleep-deprived state. From the viewpoint of CO and blood pressure, Sagawa reported a schematic expression of the time-deprived state. From the viewpoint of CO and blood pressure and BNP secretion,12 Our present study revealed that exercise-induced changes of plasma ANP or BNP concentration will be the subject of further study including evaluation of actual left ventricular function, peripheral venous function, and extracellular fluid volume during chronic sleep deprivation.

Clinical Implication of the Study

These results support the hypothesis that a clinical evaluation of left ventricular dysfunction, which uses the values of plasma ANP or BNP concentration to estimate the degree of dysfunction, could underestimate the dysfunction if the subject is in a state of chronic sleep deprivation.

Study Limitations

In the present study, hemodynamic monitoring such as pulmonary wedge pressure or left ventricular end-diastolic pressure and evaluation of extracellular fluid volume were not performed. Mechanisms of decrease in exercise-induced changes of plasma ANP or BNP concentration will be the subject of further study including evaluation of actual left ventricular function, peripheral venous function, and extracellular fluid volume during chronic sleep deprivation.

Conclusion

Exercise-induced changes of plasma ANP or BNP concentration are decreased due to chronic sleep deprivation.

References


