The alteration of NTproCNP plasma levels following anaerobic exercise in physically active young men

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ABSTRACT

Objective: Amino-terminal propeptide of C-type natriuretic peptide (NTproCNP) is a synthesis product of C-type natriuretic peptide (CNP). In this study, plasma levels of NTproCNP were compared before and after exercise in healthy young subjects who are physically active (PA) or not physically active (NPA).

Methods: The study was carried on PA group (n=10) who defined the exercise duration more than 2.5 hours per week for at least one year and NPA group (n=10) whose exercise duration was lower than 1.5 hours per week. The level of maximal oxygen consumption was determined. Wingate exercise test was applied on the following day. Plasma NTproCNP levels were measured before the exercise and at the 1st, 5th and 30th minute after the exercise.

Results: Exercise duration of physically active group was reported as 11.3±5.0 hours per week. Basal NTproCNP levels of the groups were found to be comparable. NTproCNP levels in the 5th minute (0.93±0.23 pmol/L; $p<0.05$) and in the 30th minute (0.77±0.21 pmol/L $p<0.05$) after exercise were higher than the levels before exercise (0.64±0.29 pmol/L) in PA group. Additionally, the plasma levels of NTproCNP after 5th minute of exercise were higher in PA group (0.93±0.23 pmol/L) than NPA group (0.74±0.16 pmol/L, $p<0.05$).

Conclusion: Being physically active may be a fact affecting the secretion of CNP, which plays a protective role in endothelium, following exercise. *(Anatolian J Cardiol 2015; 15: 97-102)*

Key words: amino-terminal propeptide of C-type natriuretic peptide, C-type natriuretic peptide, physical activity, exercise, endothelium, heart

Introduction

C-type natriuretic peptide (CNP) is a member of the natriuretic peptide family. It is present in myocardium, central nervous system, gastrointestinal and genitourinary system (1, 2). Furthermore, CNP is predominantly found in endothelial structures, protects endothelium via its effects on vascular tonus as well as regulating coagulation, development of fibrinolytic activity, suppression of thrombocyte activation and exerting antiproliferative and antihypertrophic effects (3).

It has been known that CNP is synthesized as a precursor propeptide which is divided into, biologically active CNP, and aminoterminal proCNP (NTproCNP) parts. NTproCNP has a longer halflife and greater concentrations than biologically active part. It has been reported that NTproCNP assay demonstrates more consistent and reliable data than CNP in clinical applications (4). It has been shown a significant correlation ($r=0.52$; $p<0.0001$) between plasma NTproCNP and CNP concentrations in a previous study (5). Therefore, plasma levels of NTproCNP may be related with plasma levels of CNP, because it is released from cells at equimolar ratio with this natriuretic peptide.

Biological activation of CNP is mediated by natriuretic peptide reseptors (NPR) A, B and C receptors expressed on the cell membrane. However, affinity of CNP for NPR-B receptor is higher than the other natriuretic peptide receptors. It has been known that CNP increases the concentrations of cGMP by binding to the membrane bound guanylyl cyclase, to exerts its intacellular effects (6). CNP induced vasodilation has been demonstrated in a previous study (7). This peptide, which exerts its vasodilator effect by producing hyperpolarization in vascular smooth muscle, is also defined as endothelium-derived hyperpolarizing factor (8, 9). The formation of vasodilatation results from CNP has also been observed in isolated coronary arteries (10). It has been suggested that CNP may play a role in the treatment

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of cardiac ischemic diseases (11). Therefore, to understand the possible role of exercise, as a non-drug factor directly influencing cardio-vascular function, on the plasma levels of NT-proCNP may be beneficial.

In general, studies indicates that ANP and BNP release increases in relation to exercise (12, 13). However, a discrepancy has been demonstrated in studies investigating the relationship with CNP levels and exercise in healthy people or in patients with various diseases. For instance, changes in urine levels of CNP after exercise were investigated in healthy individuals and patients with chronic heart failure in a study carried out by Bentzen et al. (14) and it has been reported that while plasma ANP and BNP levels increase, urine excretion of CNP remains unchanged. On the other hand, it has been reported by Passino et al. (15) that exercise related changes occurred in plasma CNP levels of patients with chronic health failure, and also it has been emphasized that plasma levels of CNP decreased with improvement in endothelial functions following long term aerobic exercises.

The intensity, duration and frequency of the exercise may influence the results obtained from the studies investigating the effect of exercise on CNP release. Although exercise and physical activity are considered as two similar concepts, physical activity has a wide range extending from aerobic exercises to anaerobic exercises and from mild physical activity to intense activity (16). Planned, structured and repeated physical activities can be defined as exercise. When taken into account the difficulties of classifying the exercise, it is inevitable to study on different types or durations of exercises.

Individuals who carry out moderate or intense exercise over 150 minutes weekly are classified as physically active (PA) and those who are less active described as not physically active (NPA) in guidelines for public health (16). The aim of the present study was to compare the alterations of plasma levels of NTproCNP after exercise in healthy young subjects who have varying physical activity levels.

Methods

Study groups

Twenty healthy male volunteers between ages of 18-25 years participated in this study. Healthy subjects with normal physical examination and without any pathology in electrocardiographic measurement (arrhythmia, long QT interval etc.) and in family history, whose parents have no cardiovascular disease under the age of 55, and who do not smoke were included in the present study. Subjects with hypertension, any cardiovascular disease symptoms (hypertrophic cardiomyopathy, arrhythmia, coronary artery disease, heart failure etc.), musculoskeletal system diseases and those who use drugs regularly for any kind of disease were excluded.

For all participants, daily duration of exercise was determined by a questionnaire and subjects who carry out exercise at moderate or intense level for more than two and half hours a week were included in PA group (n=10) and those who do exercises for less than one and a half hour weekly were included in NPA group (n=10). Subjects in PA groups were questioned about their daily exercise duration, the age of participation to sports, and the duration of training in active sports life, via a question form. The present study was evaluated and approved ethically by Trakya University Faculty of Medicine's Scientific Investigations Evaluation Committee.

Basal measurement and evaluations

According to the study protocol, subjects underwent a medical history and physical examination on the first day of the study. Their resting blood pressure was measured and resting ECG (Cardioline Delta 1 Plus, Bologna, Italy) was evaluated. In addition, weight and height of the participants as well as body fat ratio was determined by using bioempedance method (Tanita UM-020, Tokyo, Japan). Following these measurements, subjects were informed on the relevant issues that should be considered for exercise. Maximum oxygen consumption was determined with Astrand test on the first day of the study in order to measure the aerobic capacity of the participants.

Wingate test was performed to the participants by a bicycle ergometer for short duration and high intensity exercise on the second day of the study. Blood samples were taken from the subjects before and at 1st, 5th and 30th minutes of the exercise for determination of NTproCNP levels.

Astrand test

Maximal oxygen consumption of the individuals was measured by using Astrand test carried out with a bicycle ergometer (Monark 894-E- Monark Exercise AB, Sweden). In this test, a convenient submaximal load between 300-600 kpm/min (kilopond-meter per minute) has been chosen for participants. The experimental protocol this test consisted of having subjects pedal for six minutes against the constant load. Meanwhile, heart rate is recorded with a telemetry device via a belt worn on chest region (Polar 610i, Finland). Pedaling continued until maximum four heart beats difference observed between two consecutive minutes. Heart rate data are examined with Modified Astrand-Rhyming nomogram and maximum oxygen consumption level of participants is determined (17).

Wingate test

The aim of the present study was to investigate exercise related alterations in NTproCNP levels in blood samples. For this purpose, subjects have been done to supramaximal exercise. This exercise comprised of thirty seconds high intensity exercise during Wingate test. Prior to the onset of the test, subjects were asked to pedal for 3 minutes for warm up period. After warming up, subjects were rested for 5 minutes to improve the fatigue that can occur during this process. Then with the command of start, subjects pedaled as fast as possible against a constant load. During the test, subjects pedal against a load of 75 g/kg for thirty seconds at maximum performance and the number of rotations of pedal was determined. Subjects were

encouraged and motivated orally during the exercise period. Peak power, mean power, minimum power and fatigue index values of the participants were determined after Wingate Test, as in previous studies (18).

Determination of NTproCNP level

In order to determine NTproCNP levels before and after exercise, venous blood samples were transferred to tubes containing ethylendiamine tetraacetic acid. Blood samples were centrifuged at 3000 rotations per minute for 30 minutes and plasma separated. All NTproCNP concentrations were determined by ELISA method using enzyme immunoassay kit (NTproCNP in Plasma and Serum, Biomedica, Wien, Austria).

Blood pressure and heart rate measurement

In the present study, systolic and diastolic blood pressures of the subjects were measured by blood pressure monitor (BP 3BTO-A Microlife, Switzerland) before exercise and 1st, 5th, and 30th minutes after exercise. Heart rate values were obtained with a polar band attached to chest region (Polar 610i, Finland).

Statistical analysiss

Results were expressed as mean±standard deviation in the present study. Whether the data were distributed normally was determined by One Sample Kolmogorow-Smirnov test. Mann-Whitney U test was used for inter group comparisons and Spearman's test was used to investigate relationships between the variables. NTproCNP values in baseline, 1st, 5th, and 30th minutes in each group were compared by using Freidman test. When significant difference was found among the measurements Wilcoxon sign rank test with Bonferroni correction was used. P value <0.05 was considered as statistically significance for other comparisons. SPSS 20.0 (IBM SPSS Inc., Chicago, IL, USA) program was used for statistical analysis.

Results

It has been shown that all subjects had normal electrocardiographic findings. Age, body mass index, fat ratio and fat free mass parameters indicating body compositions of the subjects were detected in Table 1. Characteristics of sportive features of PA groups are as follows: mean age of participation to sports was 9.3±2.0 year and mean year of duration of training was 12.4±2.1. It has been also established that mean duration of weekly sports practice was 11.3±5.0 hours. None of the subjects were declared to do sporting activity in NPA group.

Maximum oxygen consumption, peak power, mean power, minimum power, fatigue index

Maximum oxygen consumption of the subjects in both groups has been determined with Astrand test and data were demonstrated in Table 2. It has been observed that maximum oxygen consumption was not statistically different in PA group than NPA group. In the present study, peak power, mean power, minimum power and fatigue index values were determined following Wingate test, and no significant difference has been found between two groups with regard to these measurements (Table 2).

Table 1. Demographic, anthropometric and body composition characteristics of groups

	PA group (n=10)	NPA group (n=10)	*P*
Age, year	22.4±2.8	21.9±0.8	0.61
BMI, kg/m^2	26.5±5.4	23.6±3.8	0.16
Fat ratio (%)	19.1±7.2	15.4±7.2	0.24
Fat free mass ratio (%)	58.9±8.0	59.0±4.9	0.83

BMI - body mass index; NPA - not physically active; PA - physically active; Values were shown as mean±SD in PA ve NPA groups. *P* values *P*<0.05 accepted as statistically significant

Table 2. Measurements of maximal oxygen consumption, peak power, mean power, minimum power, fatique index of groups

	PA group (n=10)	NPA group (n=10)	*P*
VO_2 Max, mL/kg/dk	38.2±7.0	35.0±6.8	0.49
Peak power, w/kg	12.6±5.3	10.9±2.2	0.87
Mean power, w/kg	6.4±0.5	6.6±0.7	0.36
Minimum power, w/kg	4.3±1.2	4.0±1.1	0.25
Fatigue index, w/kg	59.4±15.3	62.7±8.3	0.16

NPA - not physically active; PA - physically active; VO_2 Max-maximal oxygen consumption; Values were shown as mean±SD in PA ve NPA groups. *P* values *P*<0.05 accepted as statistically significant

NTproCNP levels

In the present study, values of NTproCNP were determined in blood samples drawn before exercise (C-0), one minute after exercise (C-1), five minutes after exercise (C-5) and thirty minutes after exercise (C-30; Fig. 1). When comparison to C-0, C-1 and C-30 values of NTproCNP between two groups, no significant difference has been found (respectively; p=0.08, p=0.17 and p=0.67). However, C-5 values of NTproCNP were found higher in PA group than NPA group (p=0.02; Fig. 1).

NTproCNP values were not found different between C-0 and C-1 for intra group comparison of PA group. However there was an increase in NTproCNP levels of C-5 and C-30 in comparison to C-0 (Fig. 1). NTproCNP measurements at C-5 and C-30 were found to be higher than those at C-1 in PA group (respectively p<0.01 and p<0.01). Additionally, NTproCNP measurements at C-5 were found to be higher than those at C-30 (p<0.01). As to NTproCNP levels in NPA group, no significant difference was found between values at C-0 and those at C-1, C-5 and C-30 (respectively p=0.20, p=0.76, p=0.57).

In PA group no significant relation was found between NTproCNP values at time points of C-0, C-1, C-5 and C-30 and maximum oxygen consumption (respectively, p<0.01 and r=0.01; p=0.62 and r=-0.17; p=0.80 and r=-0.09; p=0.52 and r=-0.22) in the present study. Likewise, in NPA group, no significant relation was found between values at C-0 (p=0.28 and r=-0.37), C-1

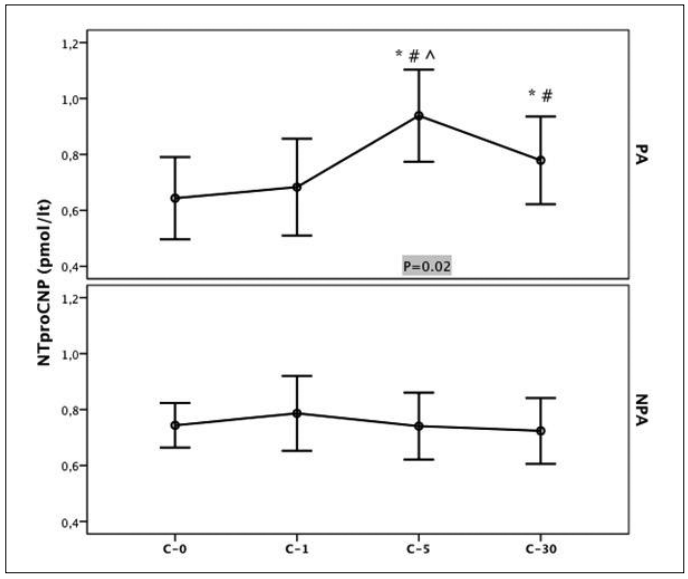

Figure 1. Plasma NT-pro CNP values before exercise (C-0), one minute after exercise (C-1), five minute after exercise (C-5), and thirty minute after exercise (C-30). *; significant difference from C-0, #; significant difference from C-1, ^ ; significant difference from C30

(p=0.14 and r=-0.49), C-5 (p=0.56 and r=-0.20) and C-30 (p=0.56 and r=-0.20) and maximum oxygen consumption.

Systolic, diastolic blood pressure and heart rate

In the comparison of systolic blood pressure (SBP) between PA and NPA groups, it was established that SBP-0, SBP-1, SBP-5 and SBP-30 values were not different (respectively; p=0.59, p=0.07, p=0.15 p=0.13; Fig. 2). Similarly, in the comparison of diastolic blood pressure, no significant difference was found between groups in terms of, DBP-0, DBP-1, DBP-5 and DBP-30 values (respectively p=0.76,p=0.06, p=0.38, p=0.18).

In the present study, in PA groups, it was found that, SBP-1 measurements were significantly increased compared to SBP-0, SBP-5 and SBP-30 (respectively p=0.01, p<0.01 and p<0.01; Fig. 2). Therefore, in PA group, when the association between 5th minute increase in NTproCNP and SBP-1 measurement was evaluated, no statistically significant relation was found between them. It was recognized that only 15% of the change in NTproCNP (adjusted R^2=0.15) could be attributed to the increase in systolic and diastolic blood pressure. SBP-0 values were not significantly different from SBP-5 and SBP-30 values (respectively, p=0.54 and p=0.16).

In NPA group, it was established that SBP-1 level was higher than, SBP-0 and SBP-30 values (respectively p<0.01 and p<0.01; Fig. 2). SBP-0 values were found to be similar to SBP-5 (p=0.21). It was also seen that SBP-1 values were higher than SBP-5 and SBP-30 value (p<0.01 and p<0.01). In the comparison of SBP-5 values with SBP-30 values, SBP-5 values were found to be higher (p<0.01).

In the comparison of heart rate between groups, it was established that values before and one, five and thirty minutes after exercise were similar (respectively; p=0.25, p=0.25, p=0.09 and p=0.06).

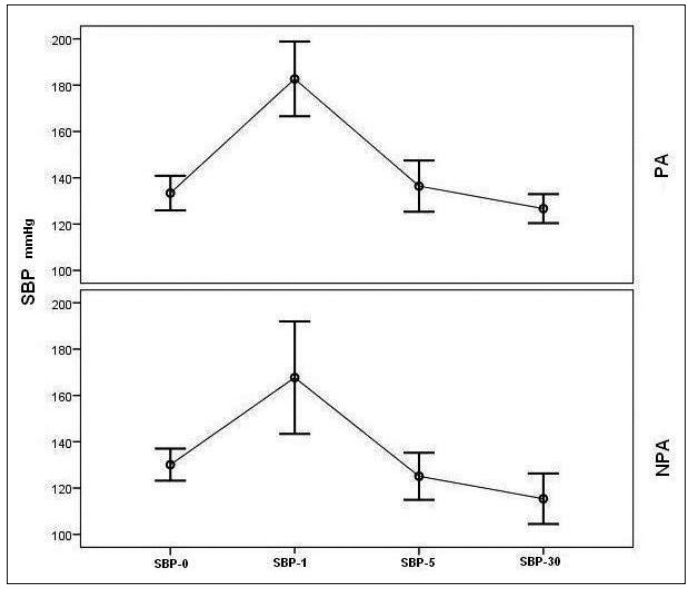

Figure 2. The alterations of systolic blood pressure (SBP) levels before exercise (SBP-0), one minute after exercise (SBP-1), five minute after exercise (SBP-5), thirty minute after exercise (SBP-30). *; significant difference from SBP-0, #; significant difference from SBP-5, ^; significant difference from SBP-30

Discussion

The results of the present study demonstrate that plasma levels of NTproCNP increases after exercise in subjects who are PA but not in NPA subjects. However, alteration in NTproCNP following exercise was not found to be associated with the changes in systolic and diastolic blood pressure.

CNP is a natriuretic peptide produced by vascular endothelium (19). It is known that paracrine and autocrine effects of this peptide are important rather than its endocrine effects (20). However, the findings of the present study demonstrated that plasma levels of CNP increased at fifth minute after exercise and this increase was continued until thirty minutes after exercise. Therefore, it is possible that regular physiological activity may be a factor influencing endothelial CNP release following acute exercise.

Increased CNP concentrations following exercise may exert various endocrine effects by binding to natriuretic peptide receptors in the body. For instance, it has been reported that CNP act as an antihypertrophic agent in myocardial tissue (21). When considered long lasting exercise periods may lead to development of cardiac hypertrophy, it has been thought that increase in CNP in PA subjects following exercise, may play a role in cardiac adaptation in response to exercise. On the other hand, it has been demonstrated that CNP exerts antifibrotic and antiproliferative effects in myocardial tissue. It has been reported that cardiac fibrosis decreased markedly after infusion of CNP for 14 days in rats who have acute myocardial infarction (22). Additionally, it is known that antifibrotic effect of CNP is mediated by cGMP (23). The relationship between plasma CNP levels and left ventricle fibrosis has been investigated in a previ-

ous study (24). It has been reported a relationship between the level of CNP in circulation and left ventricle fibrosis. It is known that left ventricle fibrosis is a strong sign of cardiac aging. In addition, high levels of CNP results in antiproliferative effects in cardiac fibroblasts (24). In the present study, it is possible that exercise associated increase was shown in NTproCNP therefore the findings of this study considered that CNP may play a role in decreasing fibrotic effect related to cardiac aging in PA group. Findings of the present study suggest that possible antifibrotic effects of post exercise increase in plasma CNP levels on cardiac fibroblast should be investigate by further studies.

Other cardiovascular effects of CNP are the decrease in cardiac filling pressure due to the relaxation of vessels and decrease in venous return (25). In the present study, however, no difference was found in blood pressure in association with the increase in CNP levels after exercise, between PA and NPA groups.

The present study was carried out on two groups as PA subjects and those who are NPA. Physical activity levels were determined based on self-reports of the individuals. Physical activity is defined as body movements which bring about increase in energy expenditure in relation to the contraction of skeletal muscles. Subjects who are doing moderate or vigorous physical activity more than 150 minute in a week describes as physically active (16). When aerobic performance of two groups was investigated in the present study, it was established that maximal oxygen consumption was not significantly higher in PA group than NPA group (Table 2). It was also found that values did not differ after tests helping to evaluate anaerobic performance such as peak power, mean power and minimum power obtained by Wingate test in this study. Therefore, no statistically significant difference was found between subjects with regard to aerobic and anaerobic capacity. This finding has been considered as evidence that although healthy people are not markedly different aerobic or anaerobic capacities, their physical activity may lead to an increase in NTproCNP release.

CNP is similar to other natriuretic peptides, in terms of structure and function. In the evaluation of the response of natriuretic peptide to exercise, ANP plasma level was not investigated in the present study in addition to plasma NTproCNP level. However, it has been established in a previous study that plasma ANP levels increased within five minutes after exercise in healthy individuals (26). On the other hand, some studies have not been reported any increase in plasma BNP level after exercise in healthy individuals (27, 28). In addition, the response of BNP to exercise seems to be associated with high sodium levels. It has been reported in healthy subjects that BNP levels increased substantially during exercise in relation to high sodium intake for five days (29). According to findings of this study, exercise related changes in CNP levels were similar to ANP levels in PA group but not in NPA group.

Study limitations

In the present study, plasma CNP levels were measured indirectly by the examination of NTproCNP levels. Although it has been shown the relationship between NTproCNP and CNP synthesis, different clearance pathways of NTproCNP and CNP should also take into account. Thus, further studies are needed to investigate whether increased NTproCNP levels could result from decreased NTproCNP clearance in PA groups. However, estimation of NTproCNP, which is larger and has a longer half life, is thought to be rational method in the indirect determination of CNP (5).

Conclusion

In conclusion, alterations in plasma NTproCNP levels following exercise were compared between physically active and non-physically active healthy young males in the present study. For this purpose, subjects were submitted to bicycle exercise requiring pedaling against a certain load for a short and intense exercise. The findings of this study indicated that there were no differences in NTproCNP levels in resting conditions between two groups (p=0.08). However, it was established that NTproCNP levels following five minutes exercise were higher in PA group than NPA group (p=0.02). These findings indicated that NTproCNP release following short term and intense exercise period is different in PA group than NPA group.

Possible antifibrotic, antihypertrophic and vascular tonus changes which were result from the increase in plasma CNP levels following exercise in PA subjects should be investigated by further studies, which will help to understand the role of CNP in cardiac aging, cardiac hypertrophy and regulation of blood pressure.

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