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Influence of Altitude Training on Brain Natriuretic Peptide and Atrial Natriuretic Peptide in Japanese Collegiate Swimmers

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Abstract

Objective and method: To examine the effect of altitude swimming training on BNP (Brain natriuretic peptide) and ANP (Atrial Natriuretic Peptide) levels, and evaluate if BNP and ANP can be hemodynamic markers of hypoxia- and training-induced stress, Ten collegiate swimmers (Tr) who participated in the altitude training camp at 1900m and 5 healthy subjects (Con) were participated in this study. Blood samples were obtained before the training (day0: Pre), during the training (day5: T1, 10: T2, 16: T3), and after the training (5th after descent: Post). Results: Chronologically, BNP of Tr decreased immediately after ascent and increased thereafter, however the changes were not significant. ANP levels were almost unchanged in Tr, whereas there was an increase at T1 in Con compared with Tr ($P<0.05$). BNP/ANP ratio was significantly higher in Tr ($P<0.05$) than Con at T3. The results of our study indicate that swimming training at an altitude of 1900m may influence ANP and BNP in the different way, and the stimuli of training is dominant to the hypoxic stress. Conclusion: Our results suggest that we can evaluate the training and hypoxic stress based on natriuretic peptide levels, and predict the hemodynamics or dehydration state by monitoring the natriuretic peptide levels during altitude training.

Keywords: Brain natriuretic peptide, Atrial Natriuretic Peptide, Altitude training, Swimming, dehydration.

INTRODUCTION

At present, many athletes playing various sports have undergone altitude training, and this has been the trend in Japan also. In general, athletes may experience greater physiological stress during competition and training at an altitude as compared to that at the sea level. Two of the most important physiological changes that occur are altitude-induced decrements in arterial oxyhemoglobin saturation and maximal oxygen consumption. Acclimatization as well as physiological response to high altitude, eg, hypobaric-hypoxic stimuli, can influence altitude training. Therefore, it is believed that altitude training can improve physical function by inducing erythrocytosis [1, 2, 3]. However, exhaustive altitude training is required in order to adapt to the stress and maintain the physical condition. Maladaptation to high altitude, usually 2400m above the sea level, includes high mountain sickness (HMS) and high altitude pulmonary edema (HAPE) [4]. Cardiovascular response at an altitude has been examined in some of the classic altitude studies, which were conducted at relatively high elevations (>3,100m/10,170ft) using either untrained or moderately trained subjects. Nevertheless, it is probably safe to assume that similar, but perhaps attenuated, cardiovascular responses occur in well-trained or elite athletes upon exposure to more moderate elevations where altitude training is typically conducted [3]. There are few altitude training sites in Japan, therefore almost all Japanese athletes have conducted altitude trainings in the foreign countries such as USA, Mexico, China. In 2005, we experienced a Japanese elite swimmer's sudden death during the altitude training, so we thought it was an urgent problem to confirm the physiological reaction particularly in relation to the heart at the actual altitude training.

The natriuretic peptide family proteins, including brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP), are known to regulate the body fluid balance and blood pressure; these are mainly secreted from the dilated ventricle or atrium or by myocyte stretching [5, 6, 7]. ANP secretion from the atrium is stimulated by hypoxic condition, which results in hydration by urine and causes hemoconcentration. However, the effect of altitude on BNP, which is mainly secreted from ventricle,

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causes hemoconcentration. However, the effect of altitude on BNP, which is mainly secreted from ventricle, has not been reported. The gene encoding BNP does not encode ANP [8, 9]. Furthermore, BNP was suggested to exhibit less hourly variation [10, 11] and was more sensitive to myocardial injury or cardiac function as compared to ANP [12, 13] hence, BNP has been widely used as the marker of heart failure. The main purpose of this study was to examine the effect of altitude swimming training on BNP and ANP levels, and evaluate if BNP and ANP can be hemodynamic markers of hypoxia- and training-induced stress.

METHOD

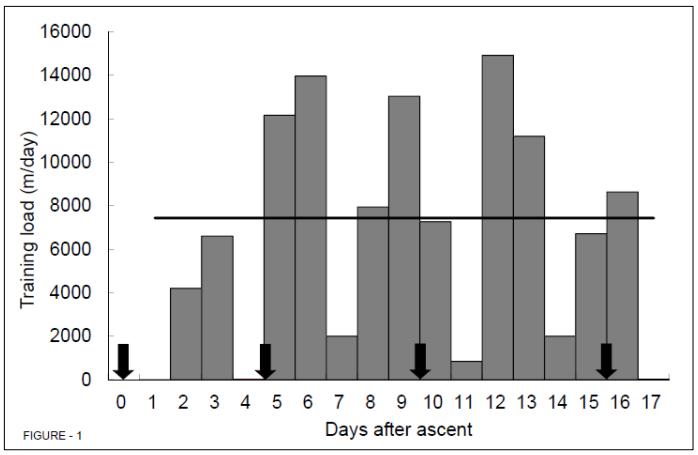
Subjects: Ten collegiate swimmers who participated in the altitude training camp were selected in the training group (Tr), whereas 5 healthy subjects were selected in the control group (Con) in this study. The swimming training camp was conducted at Kunming in China for 17 days. Kunming is located at about 1900m above the sea level. All swimmers had practiced regularly before and after the altitude training, and this was their first experience in altitude training. One swimmer was excluded from analysis because she could not undergo training because of the occurrence of a personal reason. The subjects in the Con and Tr groups were exposed to high altitude; however, the former did not exercise or had no training before, during, and after staying at high altitude. The profiles of the 2 groups are shown in Table 1. Except age, there were no significant differences between Tr and Con.

Table 1: The characteristics of the groups.

	Tr (n=9)	Con (n=5)	
Age (yr)	19.6 ± 1.2	24.6 ± 3.6	*
Height (m)	1.69 ± 0.05	1.69 ± 0.06	
Weight (Kg)	63.3 ± 4.6	67.6 ± 11.0	

Values were mean±SD. * P<0.05 between groups
There was a significant difference in age. *: *P*< 0.05

Training: The training loads are shown in Fig 1. The training was planned by experienced coaches, with reference to the previous studies of altitude training.



The average swimming training load was 7433m/day.
Blood samples were obtained before the training (day0: Pre), during the training (day5: T1, 10: T2, 16: T3), and after the training (5th after descent: Post), as shown in the arrows in the figure.

Figure 1: Daily training loads with the sampling points.

Sampling and Measurement: Blood was obtained from the vein in the forearm before（Pre, during (T1,T2,T3), and after (Post) altitude training in the morning with the subject at rest in a sitting position. Subsequently, all samples were centrifuged (2000*g*,10 min) to separate the plasma or the serum, and frozen below -20 degrees Celsius for up to 6 h. Frozen samples were transferred to the laboratories (SRL Inc, Tokyo, Japan and Kotobiken Medical Laboratories Inc, Tokyo, Japan). Plasma BNP and ANP values were determined by chemiluminescence enzyme immunoassay (CLEIA). Plasma renin activity and aldosterone concentration were analyzed by radioimmunoassay (RIA). Serum sodium (Na), serum glucose (Glucose), and serum urea nitrogen (BUN) were also analyzed, and serum osmolality (sOsm) was calculated from the osmolality equation formula below.

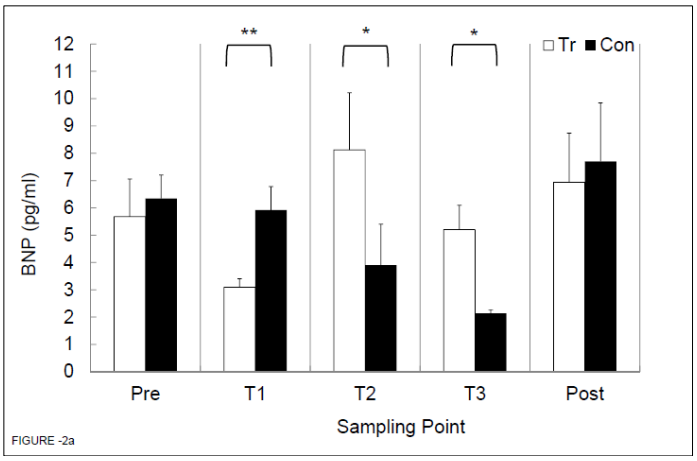
Serum osmolality (mOsm/kg)=1.86×Na+Glucose/18+BUN/2.8

Statistical analysis: Obtained data were expressed as mean±SEM unless otherwise stated, and *P*>0.05 was determined as statistically significant. With regard to ANP, BNP, and BNP/ANP values, the difference between the groups was determined by Mann-Whitney's U test and the chronological change in each group was evaluated by using Kruskal Wallis test with Steel-Dwass. Other parameters were analyzed by two-sided unpaired Student's t test and Welch's test between groups and analysis of variance (ANOVA) followed by Tukey's post hoc tests with chronological change in each group. These statistical analyses were performed by using Excel-Toukei 2006TM (Social Survey Research Information Co, Ltd, Tokyo, Japan).

Ethics: This study was approved by the Ethical Committee of University of Tsukuba Graduate School of Comprehensive Human Sciences Health and Physical Education. All subjects provided informed written consent.

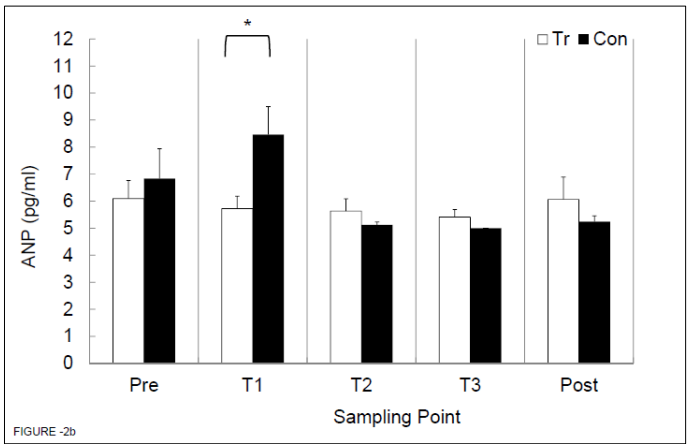
RESULT

Plasma BNP and ANP values of each group are shown in Fig 2. Chronologically, BNP of Tr decreased immediately after ascent in T1 and increased thereafter, and there was a significant increase (*P*<0.05) between T1 and T2; otherwise, there was no significant change in BNP values between the sampling points. The BNP levels of 1 subject in the Tr group were high (24.3pg/mL at T1 and 20.7 pg/mL at T3) (normal range, 0 to 18.2 pg/mL). The BNP levels in Con group gradually decreased during their stay at high altitude; however, there was no significant difference in BNP levels between the sampling points. The difference between BNP levels in Tr and Con groups was significant at T1, T2, and T3 (*P*<0.01, *P*<0.05, and *P*<0.05, respectively).



The difference between Tr and Con was significant at T1-T3 (**: *P*<0.01, *: *P*<0.05).

Figure 2a: BNP values of the Tr and Con.



Significant difference between Tr and Con at T1 (*: $P < 0.05$)

Figure 2b: ANP values of the Tr and Con.

The plasma ANP levels were almost unchanged in Tr subjects before, during, and after the altitude training. However, there was an increase in plasma ANP levels at T1 in Con compared with Tr ($P<0.05$), but the values were below 43.0 pg/mL which is the normal limit. Further, there was a decrease in plasma ANP level after T1, and there was no significant difference between plasma ANP levels in the groups after T1. The BNP/ANP ratio is shown in Fig 3. Although the chronological change in BNP/ANP from T1 and T2 was significant ($P<0.05$), no other change was obtained at altitude compared with sampling points in both the groups. Between the groups, the BNP/ANP ratio of the Tr was significantly higher than that of Con at T3.

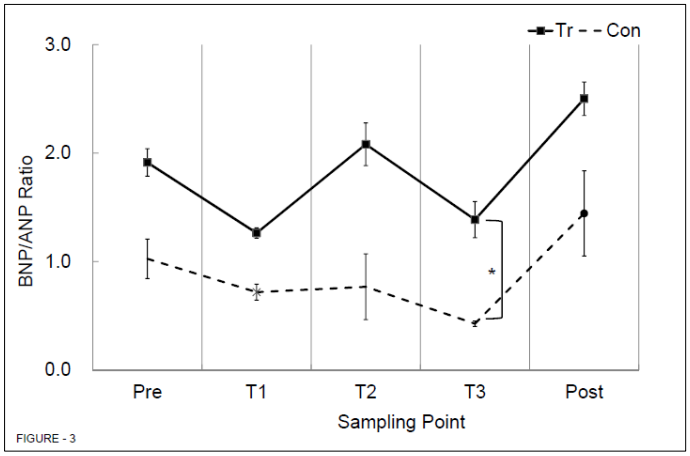


Figure 3: BNP/ANP ratio was higher in Tr at T3(*: $P<0.05$) than Con.

The data of plasma renin activity, plasma aldosterone, serum sodium, serum glucose, serum BUN, and calculated serum osmolality are summarized in Table 2. Na and sOsm at Post and BUN at T2 were different between Tr and Con. There were no chronological changes in both the groups, except that serum glucose levels at T2 and T3 of Tr were significantly lower than those at Pre.

Table 2: Plasma renin activity, plasma aldosterone concentration, serum Na, Glucose, BUN, and calculated serum osmolality.

	Pre	T1	T2	T3	Post
Plasma Renin Activity (ng/mL/hr)					
Tr	2.5 ± 0.2	4.2 ± 2.0	2.5 ± 0.3	2.0 ± 0.3	2.1 ± 0.3
Con	2.8 ± 0.4	1.8 ± 0.5	1.8 ± 0.5	1.9 ± 0.1	2.9 ± 0.2
Plasma Aldsteron (ng/dL)					
Tr	18.8 ± 3.1	19.8 ± 5.4	18.9 ± 2.4	17.0 ± 2.7	14.0 ± 1.8
Con	17.2 ± 2.0	14.3 ± 1.9	13.8 ± 1.8	15.8 ± 1.6	24.3 ± 5.9
Serum Na (mEq/L)					
Tr	139.9 ± 0.5	139.9 ± 0.4	138.7 ± 0.3	140.2 ± 0.6	139.5 ± 0.5 *
Con	140.8 ± 0.6	140 ± 0.5	141 ± 1.0	138.8 ± 1.0	137.8 ± 0.2
Serum Glucose (mg/dL)					
Tr	87.6 ± 2.6	83.4 ± 2.8	74.4 ± 3.0 #	74.4 ± 1.1 #	82.6 ± 2.7
Con	81.6 ± 4.3	78.6 ± 3.1	73 ± 2.5	73.4 ± 1.1	82.8 ± 2.6
Serum BUN (mg/dL)					
Tr	17.5 ± 1.3	14.1 ± 1.0	16.2 ± 0.8 *	14.5 ± 0.7	17.7 ± 1.6
Con	12.7 ± 1.6	12.5 ± 1.6	10.4 ± 0.8	13.5 ± 1.3	12.4 ± 0.9
Serum Osmolality (mOsm/Kg)					
Tr	271.0 ± 1.0	269.8 ± 0.7	267.8 ± 0.7	270.1 ± 1.1	270.2 ± 1.2 *
Con	270.9 ± 0.9	269.2 ± 1.1	270.0 ± 2.1	267.1 ± 2.1	265.3 ± 0.4

*: $P<0.05$ between Groups #: $P<0.05$ compared with Pre

DISCUSSION

According to our results, natriuretic peptide levels showed different responses in Tr and Con groups with change in altitude, while there were no differences between the responses of Tr and Con groups at the sea level. BNP and ANP responded differently to altitude training. BNP was higher at T3 in the late phase of the training, and BNP/ANP ratio at T3 of Con was lower than that of Tr, which implied that BNP and ANP showed different responses to altitude training. ANP increased at T1 in Con while it did not increase in Tr. There were no differences in neurohumoral and fluid balance indices such as renin activity, aldosterone, or sOsm between Tr and Con with changes in altitude.

With regard to the effect of high altitude stress on natriuretic peptide, it has been reported that there is an association between high mountain sickness (HMS) and ANP level [14, 15]; however, there have been almost no studies about the influence of altitude changes on BNP. ANP is encoded by a hypoxia-responsive gene and is secreted within 48h of hypoxic exposure [8]. Further, chronic low oxygen and pressure

can increase the ANP level; however, endurance training with altitude acclimatization attenuates the increase in ANP level [16].

The change of ANP in Con group is consistent with a previous study which reported that hypoxic stress stimulated ANP secretion [17, 18]; however, the change in Tr was not consistent with the previous reports.

Concerning the effect of exercise on natriuretic peptide levels, plasma BNP concentrations were within the normal range in all professional football players approximately 24h after a football training session [19]. In the study of ultra-endurance triathlon, BNP increased in every athlete and the mean increased significantly (12.2 vs 42.5 ng/L; P<0.001) after the exercise [20]. Swimming induces the release of ANP mainly from the right atrium to plasma, with the recovery of ANP in the right atrium requiring almost 1 day in rats [21].

The normal value of BNP was determined by studies on healthy subjects over 50 years old, and the range is reported to increase with age [22, 23]. In this study, ANP and BNP levels were measured using immunoradiometric assays based on a 2-site sandwich antibody system (Shionogi, Japan). Wang *et al*. reported almost the same upper reference limits for BNP in subjects between 20 and 49 years and those between 50 and 59 years. In this study, there was significant difference between the average age in subjects of Con and Tr groups; however, the influence of age on the values of natriuretic peptides was negligible. Based on the data of college athletes, the median BNP level was 8 pg/mL and there was a weak correlation between BNP level and exercise training load [11].

Further, some investigators suggest that BNP/ANP value is more sensitive and can be used to predict heart failure or other heart diseases [24, 25, 26, 27]. Hence, we measured the natriuretic peptide during altitude training after overnight fast in the morning. There was a very small increase in BNP induced by exercise in a patient with congestive heart failure (CHF) [28], and BNP levels showed only minor changes with vigorous exercise. Therefore, it is unlikely to classify normal subjects as having CHF based on the BNP level obtained after activity [29]. Since prior activity does not influence BNP levels in patients with CHF, a marked change in the BNP level of patients may reflect a real change in their condition [29]. We hypothesized that BNP and BNP/ANP should be strong indicators of the heart function.

Further, ANP level was elevated on the 21st day after ascent in rats, and the expression of ANP/BNP mRNA was enhanced by hypobaric-hypoxic stimuli and also by endurance exercise [30]. The decreased ANP during sub maximal exercise after altitude acclimatization and the time course of ANP appears to be different from that of plasma renin activity and aldosterone [31, 32].

ANP was mostly affected by exercise intensity and to a lesser extent by exercise duration; hypoxia had no effect on ANP at rest and reduced the exercise response [33]; and extended ANP response was observed in a severe state of dehydration was not restored by water intake during the workload [34].

Hence, the first interest of this study was to determine the interaction between natriuretic peptide and altitude-induced hypoxic stress and exercise stress, and the second to evaluate whether there is a difference in the ANP and BNP levels in response to the altitude and exercise stress.

A previous study reported that the changes in ANP and BNP syntheses in the cardiac tissues of rats showed similar response to hypobaric hypoxic environment [35]. ANP was stimulated by hypobaric hypoxic stress; hence, ANP of Con group was elevated in T1; in contrast, there might not be hypervolemia causing elastic stimula of light ventriclein Tr, and the training suppressed the ANP and BNP elevation in Tr. In the case of impairment of heart function, BNP expression should be dominant, and consequently the training load might impose the stress on the heart of Tr in T3. Hence, we suggest that ANP and BNP were mainly dependent on the training stress rather than on hypobaric-hypoxia and that ANP secretion at rest after ascent might be suppressed by training or other various stresses such as dehydration.

The training intensity was appropriate from the safety point of view, because no ANP and BNP values were above the normal upper limit. This result was not consistent with the previously reported finding that climbing at high altitude or exercise induced an increase in natriuretic peptide [14, 30]. Previous studies have been conducted at 2000m above the sea level, while in this study training was conducted at 2000m below the sea level. Cardiovascular responses at an altitude have been evaluated in some of the classic altitude studies, which were conducted at relatively high elevations (>3100m) using either untrained or moderately trained subjects. Nevertheless, cardiovascular responses were observed in well-trained or elite athletes upon exposure to more moderate elevations [3].

We suggest that natriuretic peptide can be helpful for the management of altitude training and to determine the deconditioning, overload, or the timing of hydration during altitude training. In the altitude training, ANP increases after ascent, which causes hemoconcentration due to its diuretic effect. Therefore, in sports, ANP can be considered as a stress marker of hemodynamics or dehydration.

One limitation of this study is that we could not examine the change of ANP and BNP in the early phase of altitude training. There are no altitude training sites in Japan and we have a limited access to altitude training and large samples; further, the subject may experience hypobaric-hypoxic stress starting from the flight up to reaching the point at altitude. Furthermore, if we perform the training in an extreme artificial experimental environment or at higher altitude, the response of ANP and BNP to hypoxic stress might be clearer.

In conclusion, the results of our study indicate that swimming training at an altitude of 1900m may influence ANP and BNP in the different way, and the stimuli of training is dominant to the hypoxic stress. Our results suggest that we can evaluate the training and hypoxic stress based on natriuretic peptide levels, and predict the hemodynamics or dehydration state by monitoring the natriuretic peptide levels during altitude training.

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Conflicts of Interest

The authors declare not conflicts of interest.

REFERENCES

1. Levine BD, Stray-Gundersen J. "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. J Appl Physiol. 1997; 83(1):102-112.
2. Weil JV, Jamieson G, Brown DW, Grover RF. The red cell mass--arterial oxygen relationship in normal man. Application to patients with chronic obstructive airway disease. J Clin Invest. 1968; 47(7):1627-1639.
3. Wilber RL. Altitude training and athletic performance. Human Kinetics Publishers, Inc., IL. 2004.
4. Sherry E, Viswanathan S, Trieu L, Chisholm D, Das A. Medical problems of athletes. In: Sherry E, Wilson S (eds) Oxford Handbook of Sports Medicine Oxford University Press, New York, USA, 1998.
5. Akashi YJ, Springer J, Lainscak M, Anker SD. Atrial natriuretic peptide and related peptides. Clin Chem Lab Med. 2007; 45(10):1259-1267.

6. Liang F, Wu J, Garami M, Gardner DG. Mechanical strain increases expression of the brain natriuretic peptide gene in rat cardiac myocytes. J Biol Chem. 1997; 272(44):28050–28056.
7. Liang F, Gardner DG. Mechanical strain activates BNP gene transcription through a p38/NF-kappaB-dependent mechanism. J Clin Invest. 1999; 104(11):1603–1612.
8. Chen YF. Atrial natriuretic peptide in hypoxia. Peptides 2005; 26(6):1068–1077.
9. Tamura N, Ogawa Y, Yasoda A, Itoh H, Saito Y, Nakao K. Two cardiac natriuretic peptide genes (atrial natriuretic peptide and brain natriuretic peptide) are organized in tandem in the mouse and human genomes. J Mol Cell Cardiol. 1996; 28(8):1811–1815.
10. Clerico A, Iervasi G, Mariani G. Pathophysiologic relevance of measuring the plasma levels of cardiac natriuretic peptide hormones in humans. Horm Metab Res. 1999; 31(9):487–498.
11. Daniels LB, Allison MA, Clopton P, Redwine L, Siecke N, Taylor K, *et al*. Use of natriuretic peptides in pre-participation screening of college athletes. Int J Cardiol. 2008; 124(3):411–414.
12. deLemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003; 362(9380):316–322.
13. Steele IC, McDowell G, Moore A, Campbell NP, Shaw C, Buchanan KD, *et al*. Responses of atrial natriuretic peptide and brain natriuretic peptide to exercise in patients with chronic heart failure and normal control subjects. Eur J Clin Invest. 1997; 27(4):270–276.
14. Bartsch P, Shaw S, Franciolli M, Gnadinger MP, Weidmann P. Atrial natriuretic peptide in acute mountain sickness. J Appl Physiol. 1988; 65(5):1929–1937.
15. Loeppky JA, Icenogle MV, Maes D, Riboni K, Hinghofer-Szalkay H, Roach RC. Early fluid retention and severe acute mountain sickness. J Appl Physiol. 2005; 98(2):591–597.
16. Hou XH, Sun XH, Ge XF. The effects of "living high training low" on plasma ANP and cardinal function of rats. J Wuhan InstPhys Educ. 2000; doi: cnki:ISSN:42-1105.0.2000-05-027.
17. Ljusegren ME, Andersson RG. Hypoxia induces release of atrial natriuretic peptide in rat atrial tissue: a role for this peptide during low oxygen stress. Naunyn Schmiedebergs Arch Pharmacol. 1994; 350(2):189-193.
18. Toth M, Vuorinen KH, Vuolteenaho O, Hassinen IE, Uusimaa PA, Leppaluoto J, *et al*. Hypoxia stimulates release of ANP and BNP from perfused rat ventricular myocardium. Am J Physiol. 1994; 266(4 Pt 2):H1572- H1580.
19. Lowbeer C, Seeberger A, Gustafsson SA, Bouvier F, Hulting J. Serum cardiac troponin T, troponin I, plasma BNP and left ventricular mass index in professional football players. J Sci Med Sport. 2007; 10:291-296.
20. La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. Heart 2008; 94(7):860-866.
21. Suda K, Kato J, Nozawa M, Komabayashi T, Imai H, Era S. ANP content in rat myocardium during and after swimming. Adv Exerc Sports Physiol. 2006; 12:121–125.
22. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol. 2002; 40(5):976-982.
23. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW, *et al*. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol. 2002; 90(3):254-258.
24. Arad M, Elazar E, Shotan A, Klein R, Rabinowitz B. Brain and atrial natriuretic peptides in patients with ischemic heart disease with and without heart failure. Cardiology 1996; 87:12-17.
25. Arima M, Kanoh T, Kawano Y, Oigawa T, Yamagami S, Matsuda S. Plasma levels of brain natriuretic peptide increase in patients with idiopathic bilateral atrial dilatation. Cardiology 2002; 97(1):12-17.
26. Nicholson S, Richards M, Espiner E, Nicholls G, Yandle T. Atrial and brain natriuretic peptide response to exercise in patients with ischaemic heart disease. Clin Exp Pharmacol Physiol. 1993; 20:535-540.
27. Shimamoto K, Kusumoto M, Sakai R, Watanabe H, Ihara S, Koike N, *et al*. Usefulness of the brain natriuretic peptide to atrial natriuretic peptide ratio in determining the severity of mitral regurgitation. Can J Cardiol. 2007; 23(4):295-300.
28. Kato M, Kinugawa T, Ogino K, Endo A, Osaki S, Igawa O, *et al*. Augmented response in plasma brain natriuretic peptide to dynamic exercise in patients with left ventricular dysfunction and congestive heart failure. J Intern Med. 2000; 248(4):309-315.
29. McNairy M, Gardetto N, Clopton P, Garcia A, Krishnaswamy P, Kazanegra R, *et al*. Stability of B-type natriuretic peptide levels during exercise in patients with congestive heart failure: implications for outpatient monitoring with B-type natriuretic peptide. Am Heart J. 2002; 143(3):406-411.
30. Perhonen M, Takala TE, Vuolteenaho O, Mantymaa P, Leppaluoto J, Ruskoaho H. Induction of cardiac natriuretic peptide gene expression in rats trained in hypobaric hypoxic conditions. Am J Physiol. 1997; 273:R344-R352.
31. Bocqueraz O, Koulmann N, Guigas B, Jimenez C, Melin B. Fluid-regulatory hormone responses during cycling exercise in acute hypobaric hypoxia. Med Sci Sports Exerc. 2004; 36(10):1730–1736.
32. Rock PB, Kraemer WJ, Fulco CS, Trad LA, Malconian MK, Rose MS, *et al*. Effects of altitude acclimatization on fluid regulatory hormone response to sub maximal exercise. J Appl Physiol. 1993; 75:1208–1215.
33. Schmidt W, Brabant G, Kroger C, Strauch S, Hilgendorf A. Atrial natriuretic peptide during and after maximal and submaximal exercise under normoxic and hypoxic conditions. Eur J Appl Physiol Occup Physiol. 1990; 61(5-6):398–407.
34. Schmidt W, Rojas J, Boning D, Bernal H, Garcia S, Garcia O. Plasma-electrolytes in natives to hypoxia after marathon races at different altitudes. Med Sci Sports Exerc. 1999; 31(10):1406–1413.
35. Nakanishi K, Tajima F, Itoh H, Nakata Y, Osada H, Hama N, *et al*. Changes in atrial natriuretic peptide and brain natriuretic peptide associated with hypobaric hypoxia-induced pulmonary hypertension in rats. Virchows Arch. 2001; 439(6):808–817.