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Effect of Aerobic Activities in Hypoxia Situations on Interleukin-6 and Interleukin-10 Serums of Active Young Men

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Abstract: The purpose of this study is to investigate the effect of physical activity on cytokinesIL-6 and IL-10 in serums of human being. Eight active young men with mean age of 23.33±1.56 years old, 64.16±3.14 kg weight and 176±1.76 cm height participated in four aerobic activity sessions including running in span of 30 min with intensity of 70% maximal heart beat rate in four normoxia and hypoxia situations (at altitudes of 2750 m, 3250 m and 3750 m). Before, immediately after and 1 hour after activities, blood sample were collected. Analyzing data using mixed models indicated there isn't any significant difference between normoxia and hypoxia for concentrations of both cytokines ($P>0.05$). All of 4 activity sessions led to significant decreases in IL-6 ($P<0.05$). Also, decrease in IL-10 after activity in normoxia situation at 3250 m altitude was insignificant ($P>0.05$). Most of previous founds indicated IL-6 reduction in hypoxia situations and only one research like the present study didn't observe these reductions. Although, some probabilities have declared about this informational contrariety in the present study, but there're some evidences to deny them. There're neither in access information nor consistent results about effect of hypoxia situation on IL-10. In a manner that both increase and decrease in IL-10 were reported in hypoxia situations. In order to carry out an accurate conclusion, rather researches which control other influencing variables are required.

Key words: Hypoxia · Interleukin-6 (IL-6) · Interleukin-10 (IL-10) · Aerobic Activity · Altitude

INTRODUCTION

High altitude has not been defined precisely. Most of the individuals develop clinical, physiological and biochemical changes above 3000 m. However, there are individual variations and some people develop signs and symptoms of high altitude sickness at altitudes as low as 2000 m [1]. Others have defined high altitude arbitrarily as elevation above 2500 m [2]. Ascent to high altitude is a stressor known to alter physiologic and metabolic functions [3, 4]. There's an assumption that more improvements could be earned in people aerobic capacities by high altitude simulation. Therefore, athletes prefer to use trade devices which provide hypoxia medium [5]. Beside hypoxia situation, physical activity is a stressful condition which challenges homeostasis of body [6].

The pro-inflammatory cytokines are up-regulated by physical activity, trauma and infection. Of several known endogenous pyrogenic cytokines, IL-6 correlates most

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closely with the degree of fever [7]. Various forms of IL-6 have different biological activities [8]. Cells that express IL-6 receptors include hepatocytes, B cells, T cells, partially committed Bone marrow cells, osteocytes and various tumor cell lines [9]. Arguably, the most important effects of IL-6 are upon hepatocytes, B cells and the mononuclear phagocytes responsible for the production of IL-1 and TNF [10].

IL-6 enhances ACTH production in the anterior pituitary gland, signaling the adrenal cortex to produce glucocorticoids [11]. Which in turn, potentiate the effects of IL-6 (and other cytokines) upon hepatocytes. Negative feedback is provided by the inhibitory action of glucocorticoids on macrophages. This further down-regulates the production of IL-6, thus limiting a potentially dangerous positive feedback loop. Although IL-6 is generally regarded as a pro-inflammatory cytokine, it can play a contrary role. For example, in cancer patients, IL-6 induces the production and release of TNF binding proteins (TNF-BPs) and IL-1ra, thereby buffering the harsh effects of other indisputably pro-inflammatory cytokines [12].

Inflammation evolved both to protect the organism against infection and injury and to promote tissue repair. The anti-inflammatory cytokines (IL-4, IL-10, IL-13) attenuate inflammation by restricting inflammatory cytokine production, up-regulating their soluble antagonist binding proteins and suppressing inflammatory cell activity [13]. IL-10, like IL-4 and IL-13, is produced mainly by the TH2 subset of T cells. It is also secreted by macrophages, mast cells and B cells and is strongly implicated in immune-suppression [13,14]. IL-10 induces macrophages to diminish their NO production and it inhibits production of IFNγ by T cells and NK cells, thereby retarding development of cell-mediated inflammation [15]. IL-10 also promotes proliferation of B cells and mast cells and it acts on monocytes to induce production of IL-1ra and the soluble TNF receptor [16,17].

A few studies have examined the effect of hypoxia on the plasma IL-6 levels [18-20]. Accordingly, IL-6 has been associated with high-altitude pulmonary edema (HAPO) [18]. And recently it was hypothesized that IL-6 mediates angiogenesis [4]. With acute hypoxia (4 h), an increase in resting IL-6 plasma concentration has been demonstrated, which is unchanged over the course of acclimatization [4]. Others, however, have found no increases at 4000 m [20], or a more gradual increase to 4 d of altitude exposure [19]. Also, a short-time transient increase has been reported, i.e., the IL-6 concentration being increased after 30 h of altitude exposure but decreased to sea level values after 42 h [18]. IL-6 levels increase immediately upon arrival to altitude and remain elevated for several weeks while residing at 4300 m [4]. Thus, both acute and chronic altitude exposure results in elevated resting IL-6 levels in humans. These results are consistent with observation that the elevation in IL-6 persists while subjects are becoming acclimatized to high-altitude exposure. In contrast, a research seldom could be found which has investigated effect of hypoxia on IL-10. It's an interesting issue that these few studies represented incongruous results. Some authors recorded inhibition of IL-10 production while others recorded IL-10 increase in hypoxia situation [21, 22 respectively]. Effect of the combination of physical activity and hypoxia on IL6 and IL10 has not been sufficiently studied.

The purpose of the present study was comparison of acute responses of IL-6 and IL-10 in serum to sub-maximal aerobic activities in four hypoxia and normoxia situations corresponding to altitudes of 2750 m, 3250m and 3750 m in active young men.

MATERIALS AND METHODS

Participants: By announcement in universities of Tehran city and statement of the targets of the study, ten young active male students have been chosen purposefully in access among 23 volunteers. During the study, 2 qualified participants relinquished the research. Eight men with mean age of 23.33±1.56 years old, 176±1.76 cm height, 67.16±3.14 kg weight, maximal oxygen consuming of 48.6±3.96 (ml/body weight/min), body bulk index of 21.6±0.91 kg/height^2 and relaxation heart beat rate of 68.55±3.74 beat/min remained to the land of the research. They had at least 2 weekly regular physical activity sessions in past two years and hadn't any decease record. Also, they didn't consume medicine for curative purposes. It's necessary to be mentioned that the subject were requested to avoid consuming alcohol and caffeine in the nights before sample collecting and generally in the whole stages of the research. All steps of samples collecting were performed in the same conditions for each subject and each participant started and finished activity sessions in particular determined times, which were the same for all of this activity session.

Activity Schedule: At first, aerobic powers of the participants were measured on the treadmill using Bruce test, at the first day [23]. This session was performed in presence of physician. After 5 days, the subjects attended in the first activity sessions. Then, they performed other 4 activity session with rest intervals of 72 hr. In order to avoid misunderstanding results consequent interrupting

influences of activity sessions on each other, the sequence of the sessions' execution were chosen randomly, for each person. Each subject completed 30 min with intensity of 70% maximal heart beat rate treadmill in a manner that performed in normoxia and hypoxia situations once time and three turns, respectively. Hypoxia situations were with oxygen percentages of 15, 14 and 13 corresponding to altitudes of 2750 m, 3250 m and 3750 m, respectively. These conditions were provided by 'Go2 altitude' device (made in Australia) [24]. Correspondent altitude to normoxia situation was 1200 m in Tehran city.

Sampling and Hormonal Analysis: Before, immediately after and 1 hr after each activity session, the amounts of 5 ml blood was taken from the subjects, in sitting and constant situations. The gathered samples were poured into sterilized pipes containing K3EDTR. The heparinized pipes and EDTR were deposited into ice then remain in room temperature. After that, Serum was separated from Plasma by centrifugation for10 min at3500 RPM. All of blood samples were preserved in -20°C until sent to Lab and there, the laboratory tests were started, immediately. For each sample, IL-6 and IL-10 were estimated using Elisa method and Elisa kits with sensitivities of 0.92 (pgr/ml) and 1.0 (pgr/ml), respectively.

Statistical Analysis: All analyses were performed using SPSS 15 statistical software (SPSS Inc., Chicago, IL). Mean (Standard Deviation (SD)) were presented for quantitative variables. The normality of the study variables was tested by one-sample kolmogorov-smirnov Test. In addition, skewness and kurtosis measures have been used to confirm the results of the test due to low number of samples; since in this case the K-S test tends toward rejecting the null hypothesis of normal distribution. In significant cases were followed the results of mixed models by sidak post hoc test (Adjusted for pair wise comparisons). P- Values less than 0.05 ($p<0.05$) were considered as significant [25].

RESULTS

Values higher than 2 and 3 respectively for skewness and kurtosis measures and large values of SD for IL6 and IL10, rejected the normality of data (Tables 1 and 2) in addition with the results of the K-S tests (All $P<0.05$). Therefore the results were followed by logarithmic transformations on the variables.

For IL6, there was a significant difference within measures totally evaluated in the sessions ($F_{(8, 60)} = 11.124$, $P < 0.001$). Also, in the separate evaluation of the measurements, was observed significant differences within measurements in the all 4 sessions (All $P<0.05$) (Table 1). In addition the results of the post hoc test for normoxia (1200 m), hypoxia of different heights (2750, 3250 and 3750 m) sessions showed a significant difference between before intervention and immediately after intervention (P=0.022, P=0.003, P=0.018 and P=0.008, respectively) and also between before intervention and

Table 1: Statistics for IL6 (pg/ml) within sessions and measures and the results of the tests

Session	Measures	Mean	Std. Deviation	Skewness	Kurtosis
Normoxia (1200 m)	Before	33.41	32.35	1.25	1.96
	Immediately After	4.37	1.64	1.11	0.86
	1 Hour After	3.98	1.15	0.86	-1.06
Test results ¥		($F_{(2, 13)} = 8.795$, P = .004)			
Hypoxia (2750 m)	Before	33.30	32.04	1.22	1.88
	Immediately After	3.41	0.57	1.27	-0.26
	1 Hour After	3.50	0.83	1.35	0.55
Test results ¥		($F_{(2, 11)} = 10.591$, P = .001)			
Hypoxia (3250 m)	Before	33.36	32.05	1.22	1.85
	Immediately After	3.84	1.02	0.90	0.17
	1 Hour After	3.47	1.08	2.67	7.35
Test results ¥		($F_{(2, 13)} = 10.703$, P = .002)			
Hypoxia (3750 m)	Before	33.12	31.11	1.09	1.44
	Immediately After	3.60	0.76	0.64	-2.17
	1 Hour After	3.46	0.78	1.28	-0.16
Test results¥		($F_{(2, 12)} = 11.736$, P = .002)			
Test results§	Before	($F_{(3, 21)} = .149$, P = .929)			
	Immediately After	($F_{(3, 18)} = .929$, P = .447)			
	1 Hour After	($F_{(3, 20)} = .568$, P = .643)			

¥Based on mixed model analysis for comparing the 3 measurements within each session (after logarithmic transformation IL6)

§Based on mixed model analysis for comparing the 4 sessions separately for each measurement (after logarithmic transformation on IL6)

Table 2: Statistics for IL10 (pg/ml) within sessions and measures and the results of the tests

Session	Measures	Mean	Std. Deviation	Skewness	Kurtosis
Normoxia (1200 m)	Before	75.79	30.05	0.09	-1.19
	Immediately After	58.77	70.69	2.33	5.69
	1 Hour After	46.63	37.24	1.28	0.54
Test results ¥		($F_{(2, 15)}$ = 2.366, P = .128)			
Hypoxia (2750 m)	Before	75.79	30.05	0.09	-1.19
	Immediately After	55.34	68.18	2.35	5.60
	1 Hour After	47.56	65.29	2.60	6.91
Test results ¥		($F_{(2, 14)}$ = 3.768, P = .048)			
Hypoxia (3250 m)	Before	75.79	30.05	0.09	-1.19
	Immediately After	55.88	33.04	0.82	0.65
	1 Hour After	54.01	47.81	1.77	3.26
Test results ¥		($F_{(2, 14)}$ = 1.693, P = .219)			
Hypoxia (3750 m)	Before	75.79	30.05	0.09	-1.19
	Immediately After	42.20	41.27	1.70	1.87
	1 Hour After	37.79	28.98	1.81	3.33
Test results ¥		($F_{(2, 15)}$ = 8.896, P = .003)			
Test results §	Before	($F_{(3, 18)}$ =.153, P = .927)			
	Immediately After	($F_{(3, 19)}$ =.539, P = .662)			
	1 Hour After	($F_{(3, 20)}$ =.457, P = .716)			

¥Based on mixed model analysis for comparing the 3 measurements within each session (after logarithmic transformation IL10)

§Based on mixed model analysis for comparing the 4 sessions separately for each measurement (after logarithmic transformation on IL10)

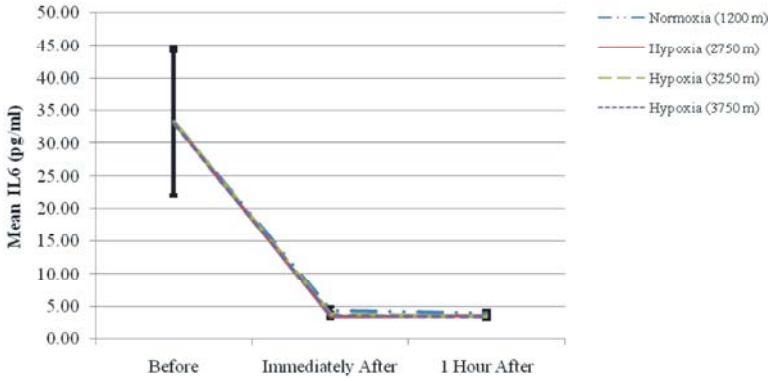

Fig. 1: Mean IL-6 (pgr/ml) in three measurements within 4 sessions

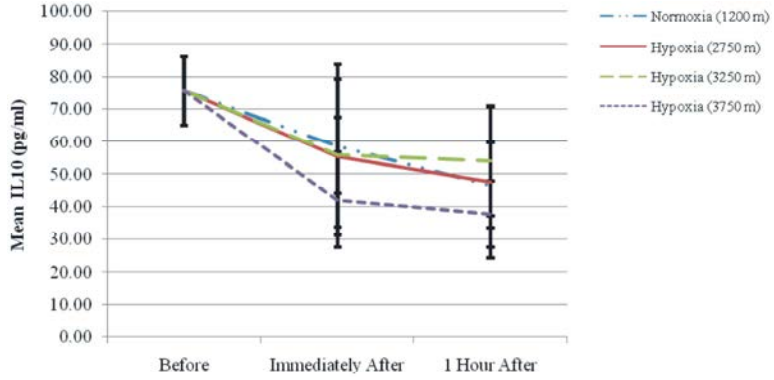

Fig. 2: Mean IL10 (pgr/ml) in three measurements within 4 sessions

one hour after intervention (P=0.003, P=0.001, P=0.001 and P=0.001, respectively). Also, there were not significant differences among sessions for before, immediately after and one hour after intervention (All P>0.05) (Table 1).

For IL10, there was a significant difference within measures totally evaluated in the sessions ($F_{(8, 63)}$ = 3.815, P = 0.001). However, in the separate evaluation of the measurements, was observed significant differences

within measurements in hypoxia (2750 m) and hypoxia (3750 m) sessions (Both $P<0.05$) (Table 2). In addition the results of the post hoc test for hypoxia (2750 m) session showed a significant difference between before intervention and one hour after intervention ($P=0.046$) and the results for hypoxia (3750 m) session showed significant differences between before intervention and one hour after intervention ($P=0.003$).

DISCUSSION AND CONCLUSION

According to results of the present study, there weren't any significant differences between IL-6 concentrations of four activity session in normoxia situations and altitudes of 2750 m, 3250 m and 3750 m, immediately and 1 hr after activity. One study has examined the effect of hypoxia on the exercise induced IL-6 [26].

Forty minutes of exercise at 50% of VO_{2max} resulted in no increase in plasma IL-6 at sea level. In contrast, exercise at the same workload increased plasma-IL-6 during acute and chronic hypoxia. Moreover, only during exercise did the exercise increase plasma IL-6. However, when the subjects were exercising at the same absolute exercise intensity (with the same workload) during hypoxic conditions as at sea level, a higher percentage of VO_{2max} was reached in accordance with the fact that VO_{2max} decreases with increasing altitude. The IL-6 response to exercise at sea level has been reported to rely on exercise intensity [27] and thus, it is likely that the increased Plasma level of IL-6 in response to exercise during hypoxia, demonstrated by Mazzeo *et al.* [4] was caused by the relative higher exercise intensity and was not caused by hypoxia as such.

Similar results were reported in cultured rat neonatal cardiac myocytes after 4 hours of hypoxia [28]. Klausen *et al.* [9] examined the influence of acute hypoxia in humans and found serum IL-6 levels to be significantly increased while other pro-inflammatory cytokines remained unchanged. It is known that the catecholamine's can act as a potent stimulator for IL-6 production and release into plasma, however, this effect has generally been thought to result from activation of the β-adrenergic pathways [29-31].

Similar findings were observed during sub-maximal exercise under conditions of both acute and chronic altitude exposure (4300 m). IL-6 levels were elevated during exercise with acute altitude exposure, likely due to the exaggerated epinephrine response associated with initial exposure to hypoxia [29].

However, founds of the present study are against too many previous understandings and indicate nonbeing difference between normoxia and hypoxia situations (up to altitude of 3750 m) in response of aerobic activities. Perhaps the differences between founds of the present study and previous understandings concern to degree of hypoxia, partially. Though, it might concern to physical activity. Niess *et al.* (2003) showed when activities done with similar relative metabolic stresses (as indicated by similar blood lactate levels), the performed activity which was done at altitude of 1800 m leads to a greater sympathetic activity in comparison with the one at sea level [32].

Also, differences between founds of the present study and understandings of previous researches partially concern to the matter that the subjects weren't carried away to the altitudes although hypoxia situations were simulated for them. Hence, variables like weather coldness, wind blowing, homesickness and etc were eliminated. Anyway, the recent statement isn't more than a guess which resulted from confusion about contrarieties in understandings and should paid attention in future. It was reported when the subjects practiced in absolute intensity of a similar activity (with a similar working load), during a hypoxia situation like sea level, higher maximal oxygen consuming percentage would be obtained in concordance with the reality of decrease in maximal oxygen consuming versus increase in altitude. Relaying on intensity of practice, IL-6 response to activity at sea level was reported [27] and so it's probable that increment of IL-6 plasma levels in response of activity in hypoxia situation, which has shown by Mazzeo *et al.* [26], might be resulted by relative high intensity of activity not by hypoxia. Only one research agreed with founds of the present study and showed insignificant at 4000 m altitudes [20]. Most of previous understandings are opposed to found of the present study and Mazzeo *et al.* [26].

In the present study, all of 4 sessions have caused significant decrease in IL-6. Indeed, the amounts of IL-6 immediately and 1 hr after activity were less before ones of before activity. This issue usually depends on intensity and span of activity and training conditions of persons. Perhaps low intensity of activity beside not long enough span of practice and the matter that the participants were active young men, have led to decreases in concentrations in each activity session. Eventually, by reviewing the literature could be guessed that one of important affecting variables is span of remaining in hypoxia situation. Maybe, remaining durations at three

altitudes of the resent study or in the other words, span of activity (30 min) an certainly 1 hr recovery after activity (60 min) which remained the subjects 90 min in hypoxia situation weren't in a limitation to be evident significant differences between hypoxia and normoxia situations up to altitude of 3750 m. Perhaps, remaining duration in hypoxia situation or span of activity are variables which have caused arising differences in results. Hence, these important variables could be rather investigated in future to answer the existing questions. According to the founds of the present study, between IL-10 concentrations of 4 activity sessions at altitudes of 2750 m, 3250 m and 3750 m weren't o bserved any significant difference. Effect of hypoxia situations on IL-10 has very less paid attention. Naldini *et al.* [21] reported that in duration of 16 hr, IL-10 production was significantly inhibited by hypoxia in both rest and activity conditions. IL-10 released 72% and 83% in rest and activity of control group, respectively. After 40 h hypoxia treatment, the results were similar [21].

However, this comparison isn't reasonable, because oxygen pressure in research of Naldini *et al.* [21] was 2%. They indicated hypoxia situation shows different pattern of cytokines production from natural pressure of oxygen. So, increment of hypoxia stimulates cytokines and inhibits release of IL-10. In contrast, Dziurla *et al.* [22] reported increment of IL-10 centesis in hypoxia situation. Also, in an interesting manner, hypoxia caused anti-inflammatory IL-10 secretion [22]. Degree of hypoxia and presence or absence of physical activity in hypoxia situation could be guessed for this informational contrariety, though there isn't any strict evidence for this relation, now. IL-10 is indicated by most of researches as an influencing factor on security suppression relating with various forms of trauma including physical activity [33,34]. Beside nonbeing change of IL-10 in hypoxia situation, there wasn't any significant difference between normoxia and hypoxia situation, up to altitude of 3750 m in the present study, although in few previous understandings increase [22] and decrease [21] in IL-6 were observed in hypoxia situations. Perhaps, the differences in results, in most important section, concern to training protocols which utilized in various researches. Also, the differences in properties of working statistical societies, especially their training condition, are in a high probably responsible to a part of inconsistency reasons in previous understandings.

Considering sub-maximal aerobic activity with intensity of 70% heart beat rate and in span of 30 min in normoxia and hypoxia situation corresponding to altitudes of 2750 m, 3250 m and 3750 m hadn't any different influence on responses of pre-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-10), in order to superior development of aerobic capacities, it's recommended active young men perform aerobic sports with hypoxia devices in possible manners. Of course, the present study prescribes this recommendation only up to altitude of 3750 m and for the mentioned activity protocol.

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