

## *Altitude, exercise and immune function*

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### **Abstract**

*Little is known with regard to how acute and chronic high altitude exposure affects immune function. Hypoxia is an environmental stressor that is known to elicit alterations in both the autonomic nervous system and endocrine function. Alterations in these systems can have an immediate as well as a longer lasting impact on immune function. Studies from the summit of Pikes Peak (4300 m) have indicated a strong  $\alpha$ - &  $\beta$ -adrenergic component in the regulation of immune function at altitude that can persist weeks after initial exposure. Specifically, interleukin (IL)-6 is elevated with acute altitude exposure primarily mediated via  $\beta$ -adrenergic stimulation and remains elevated for several weeks as a result of  $\alpha$ -adrenergic activation. When the added stress of physical exercise is combined with that of hypoxia, a more pronounced impact on immune function is observed compared to that of either exercise or hypoxia alone. A popular training paradigm currently employed by endurance athletes to enhance performance involves living at high altitude while training at low altitude. The concept entails incorporating the physiologic and metabolic adaptations associated with chronic high altitude exposure (increase in RBC, mitochondrial oxidative capacity, capillary density, etc) while training at a lower altitude allowing for the maintenance of a high absolute training intensity. Others have demonstrated that a short-term application (18 days) of the live high-train low paradigm results in suppression of the mucosal immune system as indicated by a cumulative decline in salivary IgA levels. Taken together, the majority of evidence suggests a potential additive effect of combined hypoxia and exercise in transiently suppressing immune function, at least in the short-term. Implications for the athletes and training are addressed.*

### **Introduction**

Ascent to high altitude is a stressor known to alter physiologic and metabolic functions (12-15). These adjustments to high altitude are a necessary attempt to maintain homeostasis in the presence of hypoxemia. When faced with the added stress of physical activity while at high altitude, these physiologic and metabolic responses are exacerbated. It is well documented that the sympathoadrenal pathways are activated in response to both acute and chronic high altitude exposure (12-14). It is becoming more apparent that the sympathoadrenal responses associated with

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high altitude exposure can influence many physiologic and metabolic adaptations associated with both acute and chronic high altitude exposure, including immune function (12-15). In conjunction with adrenal medullary responses, the sympathetic nervous system is associated with immunosuppression of immunocompetent cells, mobilization of T-cells and NK cells, and regulation of cytokine production and release (9,10,21).

Exercise represents an additional stress that, when combined with hypoxia, can result in a more pronounced impact on immune function than exercise or hypoxia alone. Additionally, a popular training paradigm currently employed by endurance athletes to enhance sea level performance involves living at high altitude while training at low altitude. The concept entails incorporating the physiologic and metabolic adaptations associated with chronic high altitude exposure (increase in RBC, oxygen carrying capacity, capillary density, etc) while training at a lower altitude allowing for the maintenance of a high absolute training intensity. Little is known with regard to how such training practices alter immune function and susceptibility to illness.

### Altitude is an environmental stressor

It is well known that both acute and chronic stress can adversely alter immune function. High altitude exposure is an environmental stressor that elicits neuroendocrine responses capable of influencing immune function. As one ascends to higher altitudes, the decrease in barometric pressure results in a reduction in the partial pressure of oxygen in the inspired air ( $P_I O_2$ ). As depicted in Figure 1, this initiates a sequence of physiological events leading to a reduction in arterial oxygen pressure ( $P_A O_2$ ) and content ( $C_a O_2$ ). This hypoxemia represents a major disruption in normal homeostasis thereby inducing neuroendocrine responses

designed to compensate for the reduced  $C_a O_2$ . These responses include a direct effect of hypoxia on stimulating adrenal medullary release of epinephrine, an increase in whole body and tissue specific sympathetic nerve activity and, a transient increase in circulating cortisol levels (Figure 2). An immediate benefit from these adaptations includes an increase in ventilation (helping with oxygenation of arterial blood), increased cardiac output (helping with delivery of oxygenated blood to tissues), redistribution of blood flow (ensuring critical tissues and organs get adequate oxygen) and changes in substrate selection (economical use of oxygen). In addition, it is well documented that these neuroendocrine responses have the ability to alter immune function (3,15,23,28).

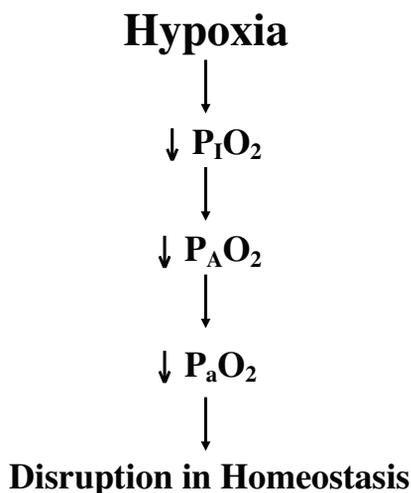
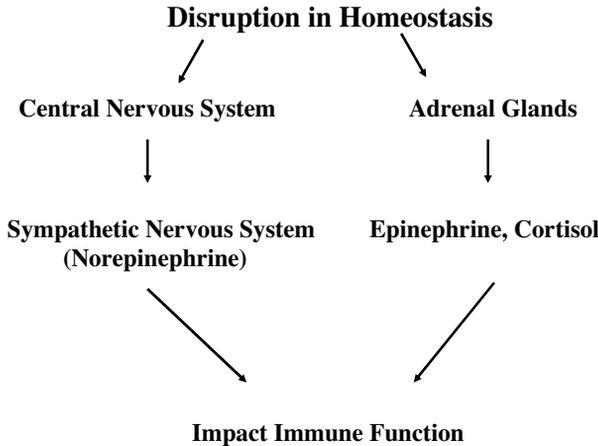


Figure 1: Sequence of events whereby hypoxia induces a disruption in homeostasis.

Our laboratory has extensively documented the sympathoadrenal responses during both acute and chronic exposure to high altitude conditions (summit of Pikes Peak, 4300 m, ~462 mmHg). We have consistently demonstrated that upon acute exposure (within 4 hrs of arrival) arterial concentrations of epinephrine are significantly elevated at rest when compared to sea level values (Figure 3). This is causally related to the direct effect of hypoxia on stimulating adrenal medullary epinephrine release. The extent of this response is dependent upon the degree and severity of hypoxia with the decline in arterial oxygen content acting as the primary stimulus. As arterial oxygen saturation improves over time during acclimatization, the hypoxic stress lessens and epinephrine levels decline approaching sea level values. Thus, an inverse relationship between  $C_aO_2$  and arterial epinephrine concentration exists.

The epinephrine response to acute high-altitude exposure is primarily mediated via the  $\beta$ -adrenergic receptors and contributes immediately to improve oxygen delivery via increases in heart rate, stroke volume (thus, increasing cardiac output), tissue vasodilation and bronchodilation. Additionally, the increase in  $\beta$ -adrenergic stimulation contributes to the elevation in metabolic rate associated with acute high-altitude exposure. The impact of the elevation in epinephrine levels on immune function is discussed below.

Unlike epinephrine, the norepinephrine response to hypoxia demonstrates a different pattern.



Plasma levels of norepinephrine are a function of the rate of spillover into the circulation of the norepinephrine released by sympathetic nervous system (SNS), and are therefore a good indicator of whole-body SNS activity. Resting levels of arterial norepinephrine during acute exposure are generally found to be similar to those observed at sea level (12-14). However, norepinephrine levels clearly rise significantly with time during more prolonged stay at altitude reaching a peak approximately

Figure 2: In response to the disruption in homeostasis caused by exposure to hypoxia, both the central nervous and endocrine systems are called upon to make adjustments to a reduction in  $C_aO_2$ . Specifically, the sympathetic nervous system and the adrenal glands play a major role improving oxygen delivery and transport during periods of hypoxia (increased cardiac output, redistribution of blood flow, alterations in substrate selection, etc). However, as a consequence of the elevation in sympathoadrenal activity, immune function can be altered.

by day 4-6. This increase in SNS activation over time at altitude has been consistently demonstrated by a variety of indicators of SNS activity (12-14).

The steady increase in SNS activity and norepinephrine levels over time primarily exert their effect via the  $\alpha$ -adrenergic receptors and directly influence local tissue blood flow, vascular resistance, blood pressure and metabolic rate. The impact of the elevation in SNS activity and norepinephrine levels on immune function is discussed below.

### Immune response to acute hypoxia

Regardless of the mechanism, it appears clear that acute exposure to altitude/hypoxia results in alterations of specific components of the immune system (4,9,10,15,16). Most prominent is the redistribution of T-lymphocytes with a notable reduction in CD4<sup>+</sup> T-cell numbers as well as an impairment in T-cell activation and proliferation (1,9,10,16). Further, acute exposure to hypoxia has been reported to result in significant lymphopenia and neutrophilia that is quite similar to that observed in response to a single bout of exercise (21,25). B-lymphocyte number and function appear to be unaltered by altitude (4,16). In total, these studies indicate the short-term hypoxic exposure results in physiological responses known to mediate immune cell trafficking and function.

Several studies have demonstrated that acute hypoxia results in increases in natural killer (NK) cell numbers and activity (9,10,21). This finding of enhanced NK cell number and activity appears to be transient as levels return to normal with more prolonged exposure to hypoxia (9,10,16). A potential mechanistic role involving the sympathoadrenal pathways was suggested. In support of this, epinephrine infusion can mimic the effect of hypoxia on NK cells while  $\beta$ -adrenergic blockade abolishes the increase in NK cell number (21).

Recently, more attention has been directed toward examining the influence of hypoxia on inflammatory cytokines. Upregulation of circulating IL-6, IL-1ra and CRP have been observed during short-term high altitude exposure and a role for these inflammatory cytokines in the development of high-altitude pulmonary edema (HAPE) has been suggested (6).

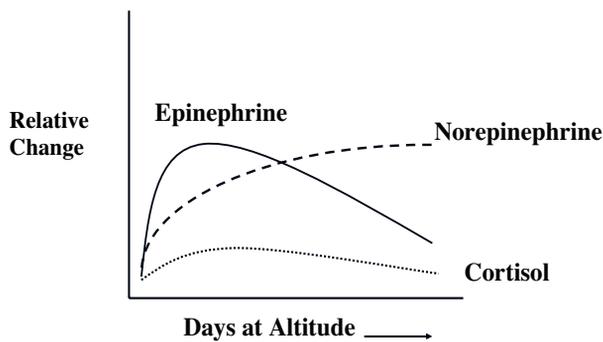


Figure 3: Typical sympathoadrenal response to both acute and chronic high altitude exposure. During initial exposure, epinephrine levels increase dramatically as a direct result of hypoxia on stimulating adrenal medullary activity. As oxygen content improves over time with acclimatization, this stimulus is lessened and epinephrine levels return toward sea level values. Sympathetic nerve activity, however, increases steadily over time at altitude as indicated by both arterial and urinary norepinephrine levels. There is a transient increase in cortisol levels with initial exposure to altitude.

It is now evident that the environmental stress of altitude/hypoxia exposure alone is sufficient to cause an elevation in circulating IL-6 even under resting conditions (independent of exercise stress). In cultured endothelial cells from mice acutely exposed to hypoxia, expression of IL-6 is dramatically increased (30). Similar results were reported in cultured rat neonatal cardiac myocytes after 4 hours of hypoxia (29). Klausen et al. (8) examined the influence of acute hypoxia in humans and found serum IL-6 levels to be significantly increased while other proinflammatory cytokines remained unchanged. As indicated in Figure 4, studies from the summit of Pikes Peak indicate that resting IL-6 levels increase immediately upon arrival to altitude and remain elevated for several weeks while residing at 4300 m (15). 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.

It is known that the catecholamines 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  $\beta$ -adrenergic pathways (3,23,28). Infusion of epinephrine has been reported to induce a dose-dependent increase in plasma IL-6 concentrations in the rat. Importantly, this epinephrine-induced increase in plasma IL-6 was blocked by the beta-adrenergic receptor antagonist propranolol (3). A separate study in rats found similar results with propranolol but also demonstrated that isoprenaline, a beta-2 adrenergic agonist, also elicited very high

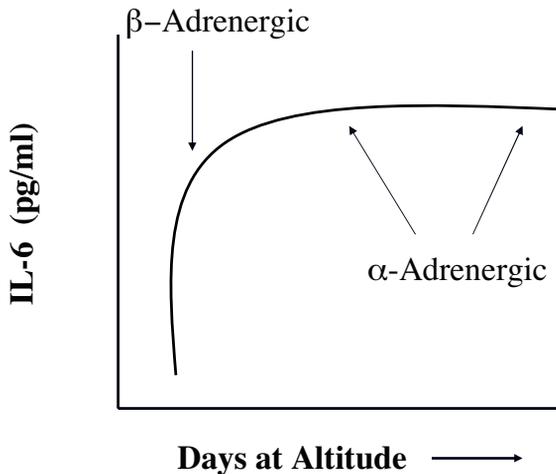


Figure 4: Interleukin-6 response to acute and chronic exposure to 4300 m. The initial dramatic increase in IL-6 levels with acute hypoxia is likely mediated via the epinephrine stimulated  $\beta$ -adrenergic pathway. As epinephrine levels decline with acclimatization, the sustained elevation in IL-6 levels appears to be a direct result of norepinephrine stimulation of the  $\alpha$ -adrenergic pathway, as  $\alpha$ -blockade completely abolishes this IL-6 response.

levels of plasma IL-6, indicating that the release of IL-6 can be mediated via the beta-2 adrenergic receptors (28).  $\beta$ -adrenergic stimulation of IL-6 production upon initial exposure to high altitude is consistent with the rapid increase in both epinephrine and IL-6 levels associated with acute hypoxia (Figures 3 & 4).

However, the fact that resting IL-6 levels remain elevated over time at altitude while epinephrine levels return toward sea level values suggest that other mechanisms must be responsible to the sustained

increase in IL-6. Recent evidence indicates that the SNS, via norepinephrine acting on the  $\alpha$ -adrenergic receptors, is a primary factor responsible to the sustained elevation in IL-6 levels over time at altitude (15). In the presence of  $\alpha$ -adrenergic blockade (prazosin), the sustained increase in resting IL-6 levels is completely abolished (15). Thus, while resting IL-6 levels remained elevated throughout the 12 days duration at altitude for the group receiving the placebo, IL-6 levels returned to sea level values by day 3 and remained there throughout the remainder of stay at altitude in subjects receiving  $\alpha$ -adrenergic blockade. Thus, the presence of  $\alpha$ -adrenergic blockade clearly influenced the IL-6 response to the chronic stress of hypoxia. The sustained elevation in IL-6 throughout the duration at altitude followed a similar pattern to that found for the increase in urinary norepinephrine excretion. Urinary norepinephrine excretion (a marker of overall sympathetic nerve activity) continued to increase steadily during days at altitude peaking at days 4-6. As norepinephrine has a strong affinity for the  $\alpha$ -adrenergic receptors, this is a potential mechanism likely to contribute to the continued elevation in plasma IL-6 levels over time at altitude, particularly in the face of declining  $\beta$ -adrenergic stimulation. This is supported by a significant correlation ( $p=0.004$ ) between resting IL-6 and urinary norepinephrine excretion rates for subjects over the course of time while at altitude (Figure 5). Other studies have reported a similar relationship between peak plasma norepinephrine and IL-6 levels during high-intensity exercise in humans (18,20).

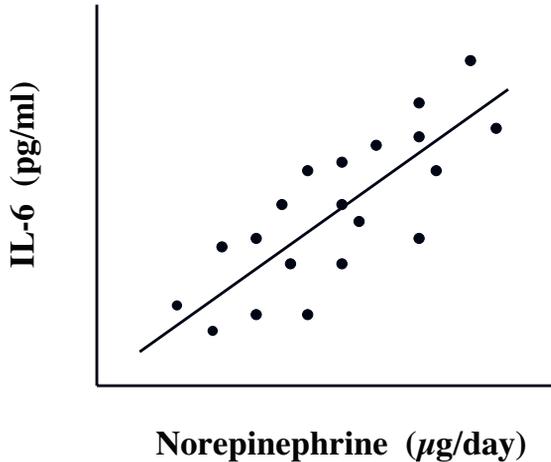


Figure 5: A significant correlation is found between the 24-hr urinary norepinephrine excretion rates over time at altitude with that of plasma IL-6 ( $r=0.43$ ;  $p=0.004$ ). Modified from Mazzeo et al., *J. Appl. Physiol.* 91:2143-2149, 2001.

The physiological significance of the IL-6 response to hypoxia remains unknown, however, a number of possibilities have been suggested. It has been suggested that IL-6 can promote angiogenesis (17) and may play a role via the induction of vascular endothelial growth factor (VEGF). Treatment of various cell lines with IL-6 for 6-48 h results in a significant induction of VEGF mRNA that is comparable to the documented induction of VEGF mRNA by hypoxia (2). Additionally, IL-6 can modulate production of erythropoietin (EPO) as the addition of IL-6 to hypoxic human hepatoma cells resulted in a dose-dependent stimulation of hypoxia-induced (EPO) production by as much as 81% (5). The associated increases in red blood cell number and oxygen carrying capacity are well-documented markers of adaptation to high altitude.

## Exercise at altitude: an added stressor

There have been numerous studies documenting the effect of a single bout of exercise on immune function (19,21,27). Generally, depending upon the exercise intensity, duration and training status of the individual, exercise has been shown to be a physical stressor that can transiently affect immune function. However, there have been only a few studies that have examined the effect of exercise while at altitude on immune function. It is likely that, even when controlling for the relative exercise intensity (as  $\text{VO}_{2\text{max}}$  and maximal performance capacity declines with ascending altitude), hypoxia represents an added stressor to that imposed by exercise alone. Klokke et al. (9) have shown that the combined effect of exercise and hypoxia result in a more dramatic effect on the NK cell response when compared to exercise in normoxic conditions. It was suggested that hypoxic exercise induces a more pronounced immunological stress response than exercise under sea level conditions.

Recently, it has been demonstrated that when exercise is performed at the same relative metabolic stress (as indicated by similar blood lactate levels), exercise performed at altitude (1800 m) resulted in greater sympathetic activation compared to sea level (18). A greater exercise-induced increase in IL-6 levels were also reported which correlated with the increase in circulating epinephrine and norepinephrine. These findings are consistent with the concept of an exacerbated immunological stress response when exercise and hypoxia are combined. Several studies have identified skeletal muscle as a potential source of circulating IL-6 during exercise and this is also likely to be the case with exercise at altitude (19,21,27).

Similar findings were observed during submaximal 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 (15). As described above, this appears to be mediated primarily via  $\beta$ -adrenergic stimulation as  $\alpha$ -adrenergic blockade had no effect in reducing the exercise-induced increase in IL-6 during acute hypoxia. However, after these subjects had acclimatized for 12 days,  $\alpha$ -adrenergic blockade significantly lowered IL-6 levels similar to those found at sea level. The group receiving the placebo still demonstrated elevated IL-6 levels during exercise suggesting a strong  $\alpha$ -adrenergic component with more prolonged residence at high altitude.

Taken together, these studies suggest an additive effect of the physical stress imposed by exercise with that of hypoxic stress. This results in a more pronounced sympathoadrenal response which has implications for immune function.

## Acclimatization & training at altitude

A number of studies have reported the benefits of altitude training for the endurance athlete with regard to improving sea level performance (7,11,24). Recently, it has been proposed that the ideal approach to maximize these benefits associated with acclimatization to altitude is the live high-train low model (11,24). This design calls for altitude exposure of at least 12-16 h/day for 3-4 weeks to elic-

it the desired adaptations (erythropoietin, red blood cell volume, etc) while returning to a lower altitude for training. Training at altitude for sea level performance is not optimal as it impairs training quality (training velocity and absolute intensity) since  $VO_{2max}$  and maximal performance capacity are reduced at altitude.

Logistically, these studies are difficult to perform do to geographic limitations. Additionally, the use of hypobaric chambers is not ideal as it can lead to a disruption in sleep and eating patterns adversely affecting training, performance and immune function. Thus, to date, only one study has examined the effect of live high-train low on immune function. Tiollier et al. (26) examined the effect of live high-train low on mucosal immunity. Highly trained cross-country skiers participated in an 18-day live high-train low training camp. The control group lived and trained at 1200 m while the live high-train low group trained at 1200 m but lived for 11 h/day in hypoxic rooms simulating an altitude of 2500, 3000 and 3500 m (six days at each altitude). Results indicated the salivary IgA concentrations decreased significantly over time in the live high-train low group but not in the control subjects. The findings suggested a cumulative adverse effect of exercise training and hypoxia on mucosal immunity over time at altitude.

When athletes live and train at altitude, the influence of hypoxia on altering immune function is evident. Pyne et al. (22) found that when members of the Australian Olympic swimming team were exposed to a 21-day training camp at 2100 m, leukocyte numbers and ConA-induced blastogenesis was reduced 38 and 32%, respectively when compared to sea level values.

Finally, it is worth noting that some studies have provided support for training high while living at low altitude. When previously untrained individuals underwent 6 weeks of altitude training at 3850 m but lived at low altitude the remainder of the day, a significant upregulation of hypoxia inducible factor 1 (HIF-1 $\alpha$  mRNA) was observed (7). No such training effect was found in subjects training under similar condition in normoxia. The combination of intense endurance training and hypoxia resulted in increases in VEGF mRNA and myoglobin mRNA suggesting hypoxic training improves various components associated with the transfer and utilization of oxygen. Impact of the train high-live low paradigm on immune function has not been investigated. Clearly, more studies need to be conducted to determine the extent to which these various training models involving altitude/hypoxia influence immune function and whether the actual susceptibility and incidence of illness is affected.

## Conclusions

It is clear that hypoxia and exercise are two independent stressors that can influence immune function. Initial exposure to hypoxia is a sufficient stressor that can elicit a neuroendocrine response that may alter immune function. While many components of the immune system are likely affected, alterations in T cell-mediated immunity are found to be the most consistent and robust. An acute bout of exercise is an added stressor at altitude that can exacerbate immune suppression, most likely through sympathoadrenal mediated pathways. An increased risk of infection is more likely during initial exposure to high altitude. As such, it would be advisable to allow athletes approximately one week to begin the acclimatization process before engaging in intense exercise training. With acclimatization, the hypoxic

stress is lessened as  $C_aO_2$  levels increase over time and adrenal medullary release of epinephrine returns towards sea level values. Consequently, T cell function approaches sea level values and the risk of infection wanes. Thus, the LHTL paradigm can be beneficial for endurance athletes and, when approached properly, should have minimal effects on immune function and illness.

Future studies are warranted and should focus on elucidating the precise mechanisms responsible for alterations in immune function during hypoxic exposure. Additionally, there is a lack of information on the time course of these immunological changes as well as the extent to which the degree of hypoxia (or altitude elevation) influence these responses. Lastly, it is important to determine the clinical significance of these hypoxia-related changes in immune function and the extent to which the risk for infection is increased.

## Considerations

Finally, a number of factors must be considered when discussing the interaction of altitude exposure and exercise on immune function. First, the altitude elevation or extent of the hypoxia is a primary factor that influences the degree of physiological stress, hormonal adjustments and immunological adaptations associated with exposure. Further, there is a minimum or threshold elevation that would be required to achieve the benefits associated with high altitude living while too high of an altitude could potentially have negative effects (sleep disruption, muscle loss) on not only immune function but performance as well. Second, the duration of stay and/or time spent at altitude will significantly impact both the extent and time course of key physiologic and metabolic adaptations associated with the acclimatization process. Additionally, it is clear that, for a given altitude, there is inter-individual variability regarding the extent of these adaptations (e.g. - red cell volume, EPO, susceptibility to altitude sickness) as well as how the hypoxic stress is perceived by the body (differences in sympathoadrenal responses). Lastly, the potential benefits from the live high:train low paradigm are going to be event and training specific and will not necessarily result in improved performance for all athletes.

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