Exercise and hypoxia: effects on leukocytes and interleukin-6—shared mechanisms?

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ABSTRACT

PEDERSEN, B. K., and A. STEENSBERG. Exercise and hypoxia: effects on leukocytes and interleukin-6—shared mechanisms? *Med. Sci. Sports Exerc.*, Vol. 34, No. 12, pp. 2004–2012, 2002. Stress-induced immunological reactions to exercise have stimulated much research into stress immunology and neuroimmunology. It has been suggested that exercise can be employed as a model of temporary immunosuppression, which occurs during physical stress, such as hypoxia. Acute exercise and acute hypoxia mediate in principle identical effects on circulating lymphocyte and neutrophil numbers. Thus, during exercise and hypoxia, lymphocytes are recruited to the blood. After the stress, the number of lymphocytes declines after the stress, whereas the neutrophil number continues to increase. When exercise is performed during hypoxia, the exercise-induced immune changes are pronounced. There is some evidence that the exercise- and hypoxia-induced changes in leukocyte subpopulations are mediated by neuroendocrinological factors such as catecholamines, growth hormone, and cortisol. In contrast, although exercise, as well as hypoxia, is associated with increased plasma levels of IL-6, the mechanisms are not likely to be the same. Thus, during exercise, contracting skeletal muscles are the main source of IL-6 production, whereas the source of IL-6 during hypoxia has not been demonstrated. The increased level of adrenaline contributes to the enormous increase in plasma IL-6 only to a minor degree during strenuous exercise. However, the only modest increase in IL-6 during hypoxia may be linked to hormonal changes, whereas the prolonged increase in IL-6 during chronic hypoxia is likely to be multifactorial. **Key Words:** PHYSICAL ACTIVITY, HIGH ALTITUDE, LYMPHOCYTES, NEUTROPHILS, IMMUNE SYSTEM, CYTOKINES

The interactions between exercise stress and the immune system provide a unique opportunity to link basic and clinical physiology, and to evaluate the role of underlying stress and immunophysiological mechanisms. It has been suggested that exercise represents a quantifiable model of physical stress (27). Many clinical physical stressors (e.g., surgery, trauma, burn, and sepsis) induce a pattern of hormonal and immunological responses that have similarities to that of exercise. This review extends earlier work on exercise immunology (7,26,35,36,50,59,74,79,80) and focuses particularly on the possibility that immune changes during acute hypoxia have common mechanisms to that observed during exercise.

EFFECTS OF ACUTE EXERCISE AND HYPOXIA ON LYMPHOCYTE SUBPOPULATIONS

Effects of exercise. Responses of blood leukocyte subpopulations to an episode of acute exercise are highly stereotyped. Neutrophil concentrations increase during and post exercise, whereas lymphocyte concentrations increase during exercise and fall below prevalues after physical work of long duration (55). Several reports describe exercise-induced changes in subsets of blood mononuclear cells (BMNC) (7,26,35,36,50,59,74,79,80). Increased lymphocyte concentration is likely due to the recruitment of all lymphocyte subpopulations to the vascular compartment: CD4+ T cells, CD8+ T cells, CD19+ B cells, CD16+ natural killer (NK) cells, and CD56+ NK cells. During exercise, the CD4/CD8 ratio decreases, reflecting the greater increase in CD8+ lymphocytes than CD4+ lymphocytes. CD4+ and CD8+ cells contain both CD45RO+ memory and CD45RA+ virgin or naive cells and "true" naive cells, which are identified by the absence of 45RO and the presence of CD62 L (3). Data show that the recruitment is primarily of CD45RO+ lymphocytes (21). Recent studies indicate that the concentrations of CD45RO+ and CD45RO-CD62 L- increase during exercise, suggesting that memory, but not naive lymphocytes, are rapidly mobilized to the blood in response to physical exercise (9). Recent studies demonstrate that after exercise, TH1 cytokine-producing cells, more than TH2 cytokine-producing cells, disappear from the circulation (96).

To obtain information about lymphocyte turnover in cells recruited during exercise, we recently analyzed telomeric terminal restriction fragment (TRF) length. Telomeres are the extreme ends of chromosomes that consist of TTAGGG repeats. After each round of cell division, telomeric sequence was lost because of the inability of DNA polymerase

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to fully replicate the 5-prime end of the chromosome. Telomere lengths have been used as a marker for replication history and the proliferation potential of the cells. Cell cultures of CD8+ T cells, which have reached replicate senescence after multiple rounds of cell division, lack expression of the CD28 co-stimulatory molecule and have short telomere lengths (9). In response to exercise, lymphocytes lacking the CD28 molecule were mobilized to the circulation, and telomere lengths in CD4+ and CD8+ lymphocytes were significantly shorter compared with cells isolated at rest (9).

NK cells are a heterogenous population that is CD3- and that express characteristic NK cell markers, such as CD16 and CD56 (61). NK cells mediate nonmajor histocompatibility complex (MHC)-restricted cytotoxicity, with potential resistance to viral infections (102) and cytolysis of some malignant cells (61). The cytolytic activity of NK cells is enhanced by interferon (IFN)-gamma (62) and IL-2 (61), whereas certain prostaglandins (PG) (8) and immune complexes (81) down regulate the function of NK cells. The *in vitro*-generated lymphokine activated killer (LAK) cells have shown a broader range of non-MHC-restricted target cell killing (23). NK and LAK cells, therefore, may play an important role in the first line of defense against acute and chronic virus infections and early recognition of tumor cells and against tumor spread (103).

Exercise of various types, durations, and intensities induces recruitment to the blood of cells expressing characteristic NK cell markers (49,82). By using *in vitro* assays, NK cell activity (lysis per fixed number of BMNC) increases consequent to the increased proportions of cells mediating non-MHC-restricted cytotoxicity. During exercise, the NK cell activity on a per NK cell basis is unchanged (60,70) or reduced (58), depending on exercise intensity.

After intense exercise of long duration, the concentration of NK cells and NK cytolytic activity declines below exercise values. Maximal reduction in NK cell concentrations, and hence the lower NK cell activity, occurs 2–4 h after exercise.

Generally, NK cell activity is increased when measured immediately after or during both moderate and intense exercise of a few minutes. The intensity, more than the duration of exercise, is responsible for the degree of increment in the number of NK cells. If the exercise has lasted for a long period and has been very intense (e.g., a triathlon race), only a modest increase in NK cells is found postexercise (86). NK cell count and the NK cell activity are markedly lower only after intense exercise of at least 1-h duration. The definitive study to map the time course in terms of postexercise NK cell immune impairment has not been done. Initial fitness level or sex does not appear to influence the magnitude of exercise-induced changes in NK cells (6,38).

Effects of hypoxia. The effect of acute hypoxia on lymphocyte subpopulations resembles the effect of exercise. Thus, when subjects were placed in a decompression chamber (380 Torr) for 20 min with or without supplemental oxygen, the lymphocyte concentration increased during the exposure and declined below prevalues in the posthypoxic period. All lymphocyte subpopulations were influenced by the hypoxia (Fig. 1A), but the CD16+ NK cells were more sensitive to the stress induced by hypoxia (Fig. 1B) (43). Also, the NK cell function demonstrated the same pattern as with exercise (Fig. 1C). The NK cell activity did not decline after the 20 min of hypoxia, which is in accordance with short-term exercise-induced recruitment of NK cells to the circulation but not poststress immune impairment. Meehan

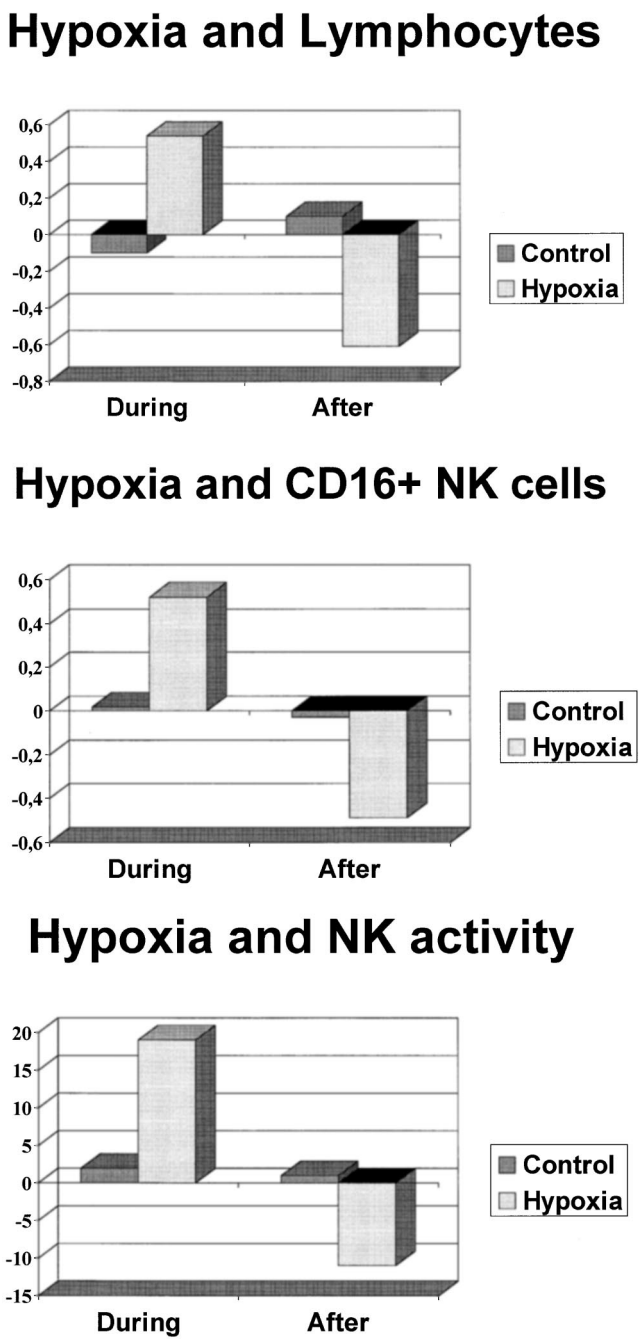

FIGURE 1—*In vivo* effect of 0.5-atm environmental pressure with (control) and without hypoxia supplementation (hypoxia) on lymphocyte concentration ($10^9 \cdot L^{-1}$ (A), CD16+ NK cells ($10^9 \cdot L^{-1}$ (B), and NK cell activity against 51Cr-labeled K562 target cells (% specific lysis per fixed number of blood mononuclear cells) (C), adapted from Klokker et al. (43)

et al. (56) demonstrated that there was no change in NK cells after 4 wk, indicating that the effect of hypoxia on NK cells is transient.

EFFECTS OF ACUTE EXERCISE AND HYPOXIA ON NEUTROPHILS

Effects of exercise. Neutrophils represent 50–60% of the total circulating leukocyte pool. These cells are part of the innate immune system, are essential for host defense, and are involved in the pathology of various inflammatory conditions. This latter inflammatory involvement reflects tissue peroxidation resulting from incomplete phagocytosis. One of the more pronounced features of physical activity on immune parameters is the prolonged neutrocytosis after acute long-term exercise (55).

There are a number of reports showing that exercise triggers a series of changes in the neutrophil population and may affect certain subpopulations differentially. Regarding the function of neutrophils, exercise has both short- and long-term effects. The neutrophil responses to infection include adherence, chemotaxis, phagocytosis, oxidative burst, degranulation, and microbial killing. In general, moderate exercise boosts neutrophil functions, including chemotaxis, phagocytosis, and oxidative-burst activity. Extreme exercise, on the other hand, reduces these functions, with the exception of chemotaxis and degranulation, which are not affected (7,63,87,88).

Effect of hypoxia. We demonstrated that hypoxia induced a small increase in neutrophil number (43). However, a marked increase in the chemiluminescence response of neutrophils was found 2 h after hypoxia (43). Thus, hypoxia and exercise induce the same effects on neutrophil number and function.

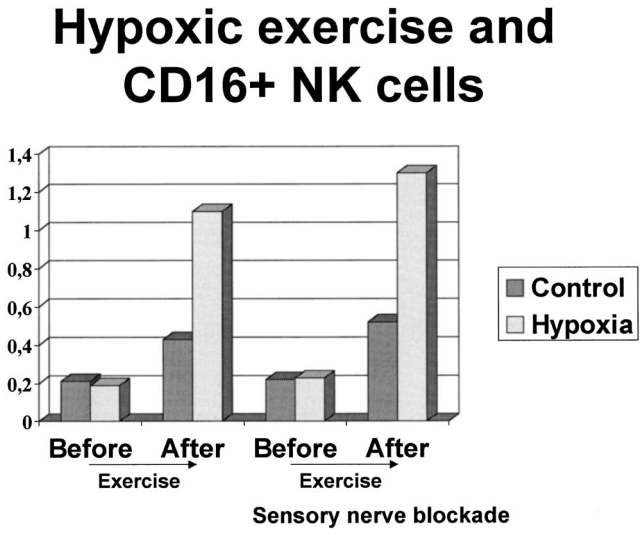

FIGURE 2—NK cell activity before and after bicycle exercise for 20 min during normoxia (control) and hypoxia. The effect of a nerve blockade, which inhibited afferent nerve impulses and the exercise-induced increase in β-endorphins is shown, adapted from Klokker et al. (44).

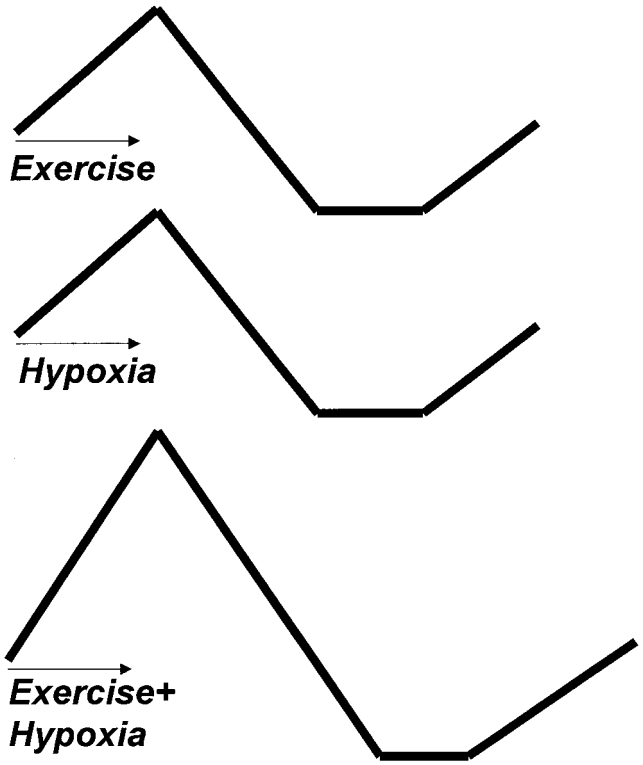

FIGURE 3—Schematic presentation of a model demonstrating the effect of exercise, hypoxia, and hypoxic exercise on lymphocyte concentration.

The combined effects of exercise and hypoxia. When exercise is performed during hypoxic conditions, the exercise-induced effects on lymphocyte subpopulations are in general pronounced (44). This was especially so regarding the combined effect of exercise and hypoxia on NK cells and NK cell function (44) (Fig. 2). Interestingly, this effect was not abolished by blocking the nerve impulses from active muscles and was not mediated by β-endorphins (Fig. 2) (44). According to our hypothesis, the effects of exercise and hypoxia may share common mechanisms. We suggest that hypoxia may add to the effect of exercise. According to this theory, hypoxic exercise will induce more pronounced stress-immunological responses compared to exercise performed during normoxic conditions (Fig. 3).

POSSIBLE MECHANISMSMS UNDERLYING LEUKOCYTE TRAFFICKING DURING EXERCISE AND HYPOXIA

The movement of neutrophils from marginal pools located intravascularly and from extravascular storage pools contributes to exercise-related neutrocytosis. The role of the lung vasculature in neutrophilic granulocyte sequestration has been demonstrated (83). With respect to the lymphocytosis of exercise, the role of margination is less clear. The spleen may contribute to a lymphocytosis because it is a major storage pool of lymphocytes, with approximately 2.5 $\times$ 10^{11} cells·d^{-1} circulating between the blood and the splenic pulpa (69). It has been demonstrated that splanchnic

sympathectomy reduces the splenic NK cell activity (34). Splenectomized subjects demonstrate a low lymphocyte count in response to injection of adrenaline (92), and subjects without a spleen show a smaller increase in lymphocyte numbers during exercise (57).

Based on the available data, we hypothesize the following model of lymphocyte recirculation with exercise and hypoxia. Lymphocytes are recruited to circulation from other tissue pools during exercise. The organs involved include the spleen, the lymph nodes, and the gastrointestinal tract. Because the cells mobilized to the blood have short telomere lengths, it is not likely that these cells are mobilized from the bone marrow or from thymus. The number of cells that enter the circulation is determined by the intensity of the stimulus. If exercise has been for a prolonged duration and/or of very high intensity, the total concentration of lymphocytes declines. The mechanisms for this probably include the lack of mature cells, which can be recruited, as well as, the redistribution of lymphocytes from the circulation to organs. In animal models (85), there is some information available about the organs to which these lymphocytes are redistributed after exercise, although the proportion of lymphocyte subsets varies as a function of lymphoid compartments. A recent animal study indicated that redistribution to skeletal muscles did not occur after exercise (17). Whether or not postexercise lymphopenia occurs is therefore dependent on a combination of intensity and duration.

The physiological basis for the neural, immune, and hormonal interactions has been extensively reviewed elsewhere (5,51,68). There are several lines of evidence suggesting that various forms of physical stressors can stimulate similar alterations in the immune system (78). Exercise is a quantifiable and reproducible stressor, which can be modified experimentally and thus considered as a prototype of stress (27). Acute, intense muscular exercise increases the concentrations of a number of stress hormones in the blood, including adrenaline, noradrenaline, growth hormone, and cortisol (22,40,101).

During exercise, adrenaline is released from the adrenal medulla, and noradrenaline is released from the sympathetic nerve terminals. Arterial plasma concentrations of adrenaline and noradrenaline increase almost linearly with duration of dynamic exercise and exponentially with intensity, when it is expressed relative to the individual's maximal oxygen uptake (40).

The expression of β-adrenoceptors on T, B, and natural killer (NK) cells, macrophages, and neutrophils in numerous species provide the molecular basis for these cells to be targets for catecholamine signaling (51). β-receptors on lymphocytes are linked intracellularly to the adenyl cyclase system for generation of cyclic adenosine monophosphate (cAMP) as a second messenger (12), and the β-adrenoceptor density appears to change in conjunction with lymphocyte activation and differentiation (1).

When adrenaline was present during preincubation of mononuclear cells as well as in the NK cell assay at adrenaline concentrations obtained during exercise, there were no significant *in vitro* effects of adrenaline on NK cells isolated before, during, or after adrenaline infusion (33). These results suggest that adrenaline may act by redistributing BMNC subsets within the body, rather than directly influencing the activity of the individual NK cells.

The numbers of adrenergic receptors on the individual lymphocyte subpopulations may determine the degree to which the cells are mobilized in response to catecholamines. In accordance with this hypothesis, it has been shown that different subpopulations of BMNC have different numbers of adrenergic receptors (39,52,84,100). NK cells contain the highest number of adrenergic receptors with CD4+ lymphocytes having the lowest number. B lymphocytes and CD8+ lymphocytes are intermediate between NK cells and CD4+ lymphocytes (52). Dynamic exercise up regulates the adrenergic density but only on NK cells (52). Interestingly, NK cells are more responsive to exercise and other stressors than any other subpopulation. CD4+ cells are less sensitive, and CD8+ cells and B cells are intermediate (27). Thus, a correlation exists between numbers of adrenergic receptors on lymphocyte subpopulations and their responsiveness to exercise.

Selective administration of adrenaline to obtain plasma concentrations comparable to those obtained during concentric cycling for 1 h at 75% of $\dot{V}O_{2max}$ mimicked the exercise-induced effect on BMNC subsets, NK cell activity, LAK cell activity, and the lymphocyte proliferative response (33,98,99). Furthermore, selective administration of adrenaline to mimic the effect of 2.5 h of treadmill running induced an immediate lymphocytosis identical to that observed during running. Adrenaline also induced poststress lymphopenia, but the decline in lymphocyte number after adrenaline only lasted 1 h. Thus, the more prolonged lymphopenia observed after running is likely to be mediated by other factors, such as cortisol. Adrenaline did not mimic the exercise effect on neutrophils. After administration of propranolol, exercise resulted in practically no increase in lymphocyte concentration (2). β1- and 2-receptor blockade, more than β1-blockade alone, inhibited head-up tilt-induced lymphocytosis and abolished the stress-induced increase in number of NK cells (45). This finding is in accordance with the fact that primarily β2-receptors are expressed on lymphocytes (4). β2-receptor blockade did not abolish the head-up tilt-induced neutrocytosis, which is in agreement with previous findings showing that adrenaline infusion caused smaller increase in neutrophil concentration than the exercise-induced increase (33,99). The effect of noradrenaline on recruitment of lymphocytes to the blood resembles that of adrenaline (31).

Adrenaline may be responsible for the recruitment of NK cells to the blood during physical exercise and other physical stress forms. The experimental basis includes the findings that 1) adrenaline infusion mimics the exercise-induced effect especially on NK and LAK cells, 2) β-adrenergic receptors are up-regulated on NK cells during exercise, and 3) β-adrenergic receptor blockade abolishes lymphocytosis during exercise and the increase in NK cell number during head-up tilt. Additional evidence comes from the observation that β2-receptor-agonists induce selective detachment

of NK cells from endothelial cells (4). Taken together, the findings strongly support the hypothesis that adrenaline strongly contributes to the recruitment of NK cells from the marginating pool in blood vessels, lymph nodes, spleen, and intestines. It is, however, very likely that the effect of acute hypoxia on lymphocytes is also mediated by catecholamines.

Growth hormone is released from the anterior pituitary in a pulsatile fashion, and irregular time courses for changes in plasma growth hormone have therefore been found. Plasma levels of pituitary hormones increase in response to exercise both with duration and intensity. Growth hormone responses are more related to the peak exercise intensity rather than to duration of exercise or total work output (40).

An intravenous bolus injection of growth hormone at blood concentrations comparable to those observed during exercise had no effect on BMNC subsets, NK cell activity, cytokine production, or lymphocyte function but induced a highly significant neutrocytosis (30). In a hyperthermia stress-model, the growth hormone release-inhibitor, somatostatin, abolished the increase in growth hormone as well as the neutrocytosis (32). Based on these observations, we propose that growth hormone does not have a major role in the exercise-induced recruitment of lymphocytes to circulation. However, growth hormone is probably mediating the initial recruitment of neutrophils to the blood during physical stress.

It has been shown that corticosteroids given intravenously to humans cause lymphocytopenia, monocytopenia, eosinopenia, and neutrophilia, which reach their maximum 4 h after administration (84). High doses of corticosteroids inhibit function of NK cells (72,76). *In vitro* studies have shown that pharmacological concentrations of methylprednisolone and hydrocortisone inhibited the NK cell function, partly by an inhibition of the adhesion of effector cells to target cells (28,75). Unlike catecholamines, however, cortisol exerts its effect with a time lag of several hours. This suggests that cortisol probably does not have a major role in the acute exercise-induced effects.

EFFECTS OF ACUTE EXERCISE AND HYPOXIA ON INTERLEUKIN-6

Effects of exercise. Exercise induces the release of a cascade of cytokines, including interleukin (IL)-6, IL-1receptor antagonist, TNF receptors, and IL-10 (16,20,77,89). In this cascade, IL-6 increases more than any other cytokine (77).

Thus, after a marathon race, IL-6 increases up to 100-fold compared with rest (66), comparable to the increases observed in patients with severe infections (11,24). The augmented plasma IL-6 after exercise was associated with muscle damage in an earlier study (10). However, recent studies have not supported this finding (14,37,65,67,93,94), and it is likely that IL-6 is produced as a direct consequence of contraction *per se* and low intramuscular glycogen stores. Plasma IL-6 during exercise increases with intensity and duration of exercise (64). Interestingly, IL-6 mRNA is up regulated in exercising human muscles (37,67,91,94) as well as in electrically stimulated rat hind limb (29).

Adrenaline has been suggested to trigger the IL-6 response during exercise (71). However, infusion of adrenaline comparable to the levels observed during exercise induces only a sixfold increase in plasma IL-6 compared with 30-fold during exercise (93). Furthermore, in another study, both an exercising and a resting leg were subjected to the same hormones, but only the exercising leg released IL-6 (94). Noradrenaline has been suggested as a potential stimulus for the exercise-induced increase in plasma IL-6 (54). Numerous studies have found that adrenaline and noradrenaline can induce IL-6 production during rest (15,93,97). However, catecholamines are not likely to play any major role in the exercise-induced IL-6 increase.

Many different cells and tissues produce IL-6, and the main sources during infections are stimulated monocytes and macrophages. A recent study demonstrated that these cells were not the source of the elevated plasma IL-6 during exercise (90). Of note, it was recently demonstrated that a contracting limb released IL-6 and that this release can account for the augmented plasma IL-6 levels (94). More recently, two studies have found that both the IL-6 release and mRNA (95) as well as the IL-6 transcription rates and mRNA (37) are further augmented when exercising with low intramuscular glycogen levels compared with control. Thus, the recent research regarding IL-6 during exercise suggests that working muscles produce and release IL-6 as a consequence of contraction *per se* and low intramuscular glycogen or altered energy turnover (37,94,95).

Effects of hypoxia. A few studies have examined the effect of hypoxia on the plasma IL-6 levels (25,41,54,73). Accordingly, IL-6 has been associated with high-altitude pulmonary edema (HAPO) (25). Furthermore, hypoxia-induced increase in plasma-IL-6 has been suggested to have a co-stimulatory effect on EPO production (41), and recently it was hypothesized that IL-6 mediates angiogenesis (54). However, on the mechanistic level, very little is known about the IL-6 response to hypoxia, and the above suggestions are mainly based on correlational relationships. With acute hypoxia (4 h), an increase in resting IL-6 plasma concentration has been demonstrated, which is unchanged over the course of acclimatization (54). Others, however, have found no increases after 1 and 2 d at 4000 m (73), or a more gradual increase to 4 d of altitude exposure (41). 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 (25). Thus, at rest, no clear and comprehensive picture of hypoxia-induced changes in the IL-6 response is yet available. However, most of the plasma IL-6 levels reported are all below the plasma levels found in response to severe infections (11,106) and within the upper normal resting values. Mazzeo and coworkers (54) demonstrated that α-adren-

ergic blockade attenuated the hypoxia induced increase in plasma IL-6. At sea level, there were no significant differences between the group receiving α-adrenergic blockade and the control group regarding plasma IL-6.

At the first day of exposure to hypoxia, plasma IL-6 increased in both groups to remarkably similar levels. The acute increase is possibly mediated by an increase in adrenaline, as adrenaline increases acutely with hypoxia (53). Later during hypoxia, the group receiving α-adrenergic blockade had significantly blunted plasma IL-6 levels compared with the controls. Moreover, plasma IL-6 only stayed elevated in the control group. In this study (54), chronic hypoxia elevated plasma IL-6 to ~ 2.5 $pg \cdot mL^{-1}$ compared with ~1.6 $pg \cdot mL^{-1}$ at sea level. Others have reported levels as high as 10 $pg \cdot mL^{-1}$ after 4 d at high altitude (41). In another study, individuals with HAPO after exposure to high altitude had plasma levels of IL-6 being >20 $pg \cdot mL^{-1}$, whereas non-HAPO individuals did not develop an increase in plasma IL-6 (42). Also, the bronchoalveolar fluid of patients with HAPO contains elevated levels of IL-6 (47). Therefore, based on data in the literature it is suggested that 1) hypoxia induces augmented plasma IL-6, mediated by increased α-adrenergic stimulation (54); and 2) that development of HAPO can result in further elevated plasma IL-6 (42). The biological importance of the nonpathophysiological elevations in plasma IL-6 found at high altitude is unknown. However, IL-6 has been shown to increase EPO production in hepatoma cells exposed to hypoxia (18) and to increase gene expression of VEGF in two different cell lines (13), suggesting a role for IL-6 in angiogenesis. Therefore, it is possible that one role of IL-6 during hypoxia is to increase oxygen availability to the different body compartments. In line with this, also hypoxia *per se* induces elevated IL-6 mRNA in cultured endothelia cells (105) and myocytes (104).

The combined effects of exercise and hypoxia. Only one study has examined the effect of hypoxia on the exercise induced IL-6 (54). Forty minutes of exercise at 50% of $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ was reached in accordance with the fact that $\dot{V}O_{2max}$ decreases with increasing altitude. The IL-6 response to exercise at sea level has been reported to rely on exercise intensity (64), and thus, it is likely that the increased plasma level of IL-6 in response to exercise during hypoxia, demonstrated by Mazzeo and coworkers (54) was caused by the relative higher exercise intensity and was not caused by hypoxia as such. When exercise intensity increases, there is a gradual shift from fat toward carbohydrate oxidation in the contracting muscle, ultimately providing 100% of substrate at $\dot{V}O_{2max}$. This increase has been shown to result mostly from an increase in muscle glycogen utilization (19). Therefore, it is likely that the same exercise protocol resulting in a higher absolute workload at hypoxia compared with sea level resulted in lower glycogen levels within the exercising muscles. This would be compatible with the finding that low concentrations of muscle glycogen stimulate a markedly higher increase in the local production of IL-6 during exercise (37,95). It has been reported that α-adrenergic blockade diminishes the augmented IL-6 response to exercise during hypoxic conditions compared with sea level (54). However, both the group receiving α-adrenergic blockade and the placebo group experienced a 62% increase in plasma IL-6. This increase was, however, significant only in the placebo group.

CONCLUSION

Based on the above studies, a model is proposed indicating possible roles of stress hormones in mediating the exercise-and hypoxia-related changes in leukocyte subpopulations. Adrenaline and to a lesser extent, noradrenaline contribute to the acute effects on lymphocyte subpopulations, NK, and LAK cell activities. The increase in growth hormone mediates the acute effects on neutrophils, whereas cortisol exerts its effects within a time lag of at least 2 h and contributes to the maintenance of lymphopenia and neutrocytosis after prolonged exercise. In contrast, although exercise, as well as hypoxia, is associated with increased plasma levels of IL-6, the mechanisms differ markedly. Thus, during exercise, contracting skeletal muscles are the main source of IL-6 production, whereas the source of IL-6 during hypoxia has not been demonstrated. Increased level of adrenaline contributes only to a minor degree to the enormous increase in plasma IL-6 during strenuous exercise. However, the only modest increase in IL-6 during hypoxia may be linked to hormonal changes, whereas the prolonged increase in IL-6 during chronic hypoxia is likely to be multifactorial. The finding that exercise-induced changes in leukocyte subpopulations and plasma-IL-6 is more pronounced when the exercise is performed during hypoxic conditions may be ascribed to that although the exercise is performed at the same work load during normoxia and hypoxia, a relative increase in intensity takes place during hypoxia. One possibility therefore exists that the more pronounced exercise-induced immunological changes during hypoxic conditions partly are a consequence of increased work intensity. However, it is also known that hypoxemia exerts a direct regulatory effect on several immune functions (i.e., PMN phagocytosis, receptor expression, and macrophage migration (46). Evidence exists that these hypoxia-induced alterations are mediated in part by specific oxygen signaling mechanisms such as HIF-1 (48), and it is suggested that these factors play also a role during exercise at altitude or under hypoxia.

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