



Brazilian Journal of Biomotricity

ISSN: 1981-6324

marcomachado@brjb.com.br

Universidade Iguauçu

Brasil

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Brazilian Journal of Biomotricity, vol. 4, núm. 2, junio, 2010, pp. 92-103

Universidade Iguauçu

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INVITED REVIEW

# IMMUNE RESPONSE TO EXERCISE

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Submitted for publication: May 2010

Accepted for publication: June 2010

**ABSTRACT**

KOCH, A. Immune Response to Exercise. *Brazilian Journal of Biomotricity*, v. 4, n. 2, p 92-103, 2010. Exercise produces transient perturbations in immunity, including alterations in circulating leukocyte numbers, cytokine concentration, and some measures of cell function. These changes are typically interpreted as being transiently detrimental to host defense. The mechanisms responsible for these immune fluctuations appear to be neuroendocrine-mediated alterations in cell-trafficking and function and microtrauma-mediated alterations in cytokine release. Alterations in immunity following exercise follow a similar pattern, but vary in magnitude depending on the volume and intensity of the exercise performed. In general, these alterations are resolved within a few hours. However, exercise induced changes in immunity may become clinically relevant after extremely prolonged bouts of exercise or repeated exercise bouts with insufficient recovery. Regular training appears to attenuate the immune response to exercise. Care should be taken to ensure that training is planned, with adequate variation in intensity and volume over time, to ensure recovery between sessions and avoid chronic systemic inflammation.

**Key words:** training, immunity, leukocytes, cytokines, immunoglobulins

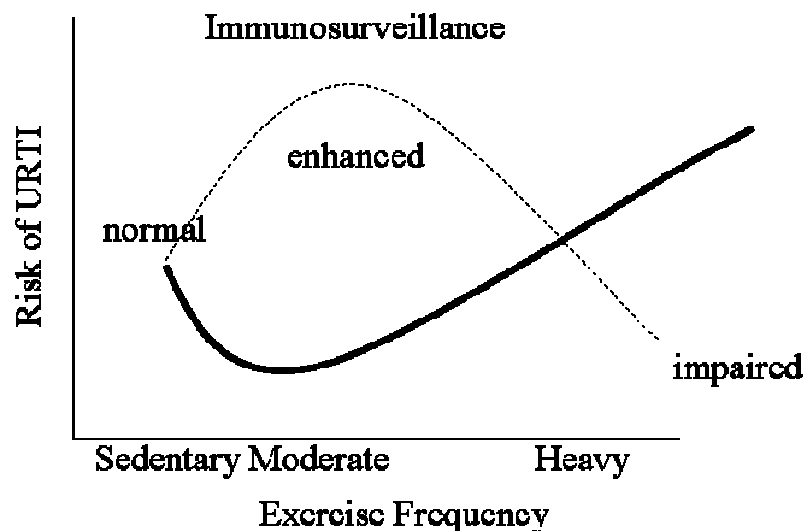
**INTRODUCTION**

Physical exercise provides a challenge to homeostasis throughout the body. The immune system, like many other physiological systems, displays substantial perturbations in response to a single bout of exercise. Many studies have documented a stereotypical immune response to vigorous exercise, consisting of a biphasic alteration in circulating immune cell numbers (BERK et al, 1990, SHINKAI et al, 1993), reduced natural killer (NK) cell activity (BERK et al, 1990), reduced mitogen-induced lymphocyte proliferation (RHIND et al, 1996), a reduced salivary immunoglobulin (Ig) secretion (NIEMAN et al, 2002), and elevated circulating cytokines (NEHLSSEN-CANNARELLA et al, 1997).

These changes in immune function are typically interpreted as being immunosuppressive, an interpretation that is bolstered by epidemiological studies of athletes versus sedentary controls. Two major mechanisms appear to drive the immune response to exercise: neuroendocrine factors and muscle damage.

### Epidemiological data

Several epidemiological studies have documented an increased risk of upper respiratory tract infection (URTI) with high volumes and intensity of endurance exercise (NIEMAN et al, 1990; HEATH et al, 1991). Based on these studies, a J-shaped curve has been postulated to explain the relationship between exercise and risk of URTI (Figure 1). According to this model, those who engage in frequent, high intensity exercise increase their odds of contracting URTI above sedentary individuals. Conversely, those who engage in moderate exercise regimens would experience fewer URTIs than sedentary individuals.



**Figure 1** - The proposed relationship between upper respiratory tract infection (URTI) risk, immunosurveillance and exercise volume.

### Circulating Leukocyte counts

Circulating leukocyte counts consistently display a characteristic, biphasic shift following heavy endurance exercise of at least 1 h duration at an intensity  $\geq 60\%$   $VO_{2max}$ . Several studies have established that high intensity aerobic exercise causes a unique, biphasic perturbation in the circulating leukocyte count (HANSEN et al, 1991). Immediately post-exercise, total leukocytes, represented evenly by neutrophils and lymphocytes, with a small contribution of monocytes, increase 50-100% above resting pre-exercise values. Within 30 min of recovery, the lymphocyte count dips 30-50% below pre-exercise levels, remaining low for 2-6 h. Eosinophils also egress from circulation, while basophils remain largely unaffected. As this occurs, circulating neutrophil numbers increase markedly and are maintained for a prolonged period. Moderate intensity exercise ( $<60\%$   $VO_{2max}$ ) has repeatedly demonstrated a much smaller degree of post-exercise leukocytosis, lymphocytosis, and neutrophilia, and a less-pronounced lymphocytopenia during recovery when compared to higher intensity activity (NIEMAN et al, 1994).

Resistance exercise studies have generally found leukocytes change in distribution in a similar manner both immediately post-exercise and during recovery to that observed during endurance exercise studies (CARLSON et al, 2008; KOCH et al, 2001; NIEMAN et al, 2004; NIEMAN et al, 1995a) despite a substantially shorter duration of effort.

The leukocytosis during and after exercise is accomplished by flushing leukocytes out of marginal pools. The mechanisms responsible for mediating this process are not fully understood, but available evidence implicates sympathetic nervous activity (NANCE & SANDERS, 2007), catecholamines (HARRIS et al, 1995), and cortisol (SHINKAI et al, 1996) as mediators of the process. Although, these changes in circulating cell numbers are thoroughly documented to occur, their clinical significance is unclear. It is not known whether the increase in circulating cells is a positive response, increasing the availability of cells to become involved in immune reactions, or if it is a negative response, meaning that cells have been diverted from areas in which they were previously involved in immune reactions. Further, the number of immune cells in circulation only reflects a small fraction (0.2%) of total leukocyte mass (GLEESON, 2007), the balance of leukocytes existing in lymphoid, bone marrow, and other tissues. Lastly, a simple accounting of circulating leukocyte number does not address the function of those cells.

### **Functions of Circulating Immune Cells**

#### *Natural Killer Cells*

Natural killer (NK) cells are large, granular lymphocytes that can mediate cytolytic reactions against neoplastic and virally infected cells. They serve as a component of the innate immune system and a first line of immune defense, as they have the cytotoxic capability without prior sensitization. NK cell cytotoxic function is commonly measured by incubating NK cells with a target cell line, then measuring the degree of cytotoxic killing by the release of radio-labeled chromium from lysed target cells.

Following prolonged (>60 min) aerobic exercise at an intensity > 60%  $VO_{2max}$ , NK cell activity (NKCA) increases immediately after exercise, but then decreases below resting values for several hours (BERK et al, 1990; NIEMAN et al, 1997) during recovery. Similarly, NKCA is substantially reduced immediately after and during at 2h of recovery following exhaustive resistance exercise employing large muscle mass, multi-joint (barbell squats) movements (NIEMAN et al, 1995a). The post-exercise increase and recovery decrease in NKCA have been attributed to the redistribution of NK cells from the circulation to other tissues (40). However, in Nieman's study (1995a), recovery NKCA was reduced even when adjusted to lytic units per NK cell, controlling for fluctuations in cell numbers. Thus it appears that intense, exhaustive resistance exercise that involves a large amount of muscle mass reduces recovery NKCA via some other mechanism, possibly prostaglandins released by activated monocytes and neutrophils (KAPPEL et al, 1991). No decrease in NK cell activity is apparent when exercise is limited to smaller muscle mass, single joint (knee extensions, calf raises) movements (FLYNN et al, 1999), likely due to the smaller metabolic and hormonal demand of such exercise.

#### *Lymphocyte proliferation*

T lymphocytes coordinate the response of many components of cell-mediated immunity via their activity and their release of many soluble factors, such as cytokines. B lymphocytes function to produce immunoglobulins, and their function is in part dependent on an interaction with T-helper cells. The functional capacity of T and B lymphocytes is commonly assessed through the proliferative response of these cells to various mitogens, such as phytohemagglutinin (PHA) and pokeweed mitogen (PWM) in vitro. When lymphocytes are exposed to a foreign pathogen, their ability to divide is an important component of the adaptive immune system. In the laboratory, researchers incubate lymphocytes with various types of mitogens and then measure the level of cellular proliferation.

The majority of studies investigating the lymphocyte proliferative response to either

intense, long endurance exercise (HENSON et al, 1998; SHINKAI et al, 1993) or heavy resistance exercise (KOCH et al, 2001; NIEMAN et al, 2004) have found a temporary impairment in the lymphocyte proliferative response following exercise. From more recent research, it appears that exercise decreases lymphocyte function after exercise through transient increases in apoptosis (programmed cell death), rather than decreases in mitosis (GREEN & ROWBOTTON, 2003; NAVALTA et al, 2007). Further, the extent of post-exercise lymphocyte apoptosis is intensity-dependent, with a threshold intensity of approximately 40-60% of  $VO_{2max}$  required to induce significantly greater apoptosis than at rest (NAVALTA et al, 2007).

#### *Neutrophil and monocyte activity*

Neutrophils and monocytes play an important role in innate or nonspecific immunity. Neutrophils comprise approximately 60% of all circulating leukocytes. They migrate to sites of infection where they bind, engulf, and destroy pathogens via phagocytosis involving both oxidative and nonoxidative means. Monocytes move from circulation to injured tissue, where they are transformed into macrophages. And when activated, becomes an integral component of both the local and systemic inflammatory process. Together, neutrophils and monocytes act as a first line of defense to eliminate infectious agents and are involved in the muscle tissue inflammatory response to exercise-induced injury (WOODS & DAVIS, 1994). Neutrophil and monocyte function can be expressed as a measure of phagocytosis (ability to engulf pathogens) or the oxidative burst (ability to kill pathogens once engulfed) (NIEMAN, 1997). Acute exercise activates phagocytic neutrophils and monocytes, increasing phagocytosis, but high-intensity activity downregulates oxidative burst activity (ROBSON et al, 1999).

### **Other components of Immunity**

#### *Cytokines*

Cytokines are soluble glycoproteins that are produced by several cell types, including immune cells, endothelial cells, and myocytes, and adipocytes. They mediate communication within and between cells, organs and organ systems throughout the body in immune, inflammatory and several other responses. Heavy physical activity produces a rapid, transient increase in cytokine production and entails increases in both pro-inflammatory (IL-2, IL-5, IL-6, IL-8,  $TNF\alpha$ ) and anti-inflammatory (IL-1ra, IL-10) cytokines (MOLDOVEANU et al, 2001).

#### *Immunoglobulins*

Immunoglobulins (Ig) are a class of glycoproteins secreted by B cells, which appear in bodily secretions, such as serum, tears, and saliva. Igs that react with a specific antigen are referred to as antibodies. Antibody serves to bind to the surface antigens of pathogens, thereby stimulating the activation and differentiation of other immune cells. There are five classes (based on basic structure) of Ig. IgG is the major class of Ig found in serum. IgA is the major Ig class found in saliva. Studies of the immunoglobulin response to exercise have focused on both serum and salivary antibodies. Salivary concentrations of IgA have been shown to correlate more closely with URTI than serum antibodies (MACKINNON & JENKINS, 1993). Salivary immunoglobulins are the first barrier to colonization by microorganisms causing URTI (TOMASI & PLAUT, 1985). Immunoglobulin A (IgA) is the predominant immunoglobulin in mucosal fluids, serving to inhibit the attachment and replication of pathogens and neutralize viruses and toxins. In addition, low resting levels of salivary IgA have been correlated with an increased risk of URTI among competitive swimmers (GLEESON et al, 1999) and American football players (FAHLMAN & ENGELS, 2005).

Some studies have found that heavy exercise can elicit a post-exercise decrease in salivary IgA levels (MACKINON & JENKINS, 1993). Suggested mechanisms behind an exercise-induced decrease in salivary IgA include changes in the transport of IgA across the mucosal epithelium or sympathetically-mediated vasoconstriction in the oral submucosa and consequent reduction in the migration of cells synthesizing and secreting IgA (REID et al, 2001).

However, this finding is not consistent, with others reporting either no change (KOCH et al, 2007) or an increase (THARP, 1991) in post-exercise IgA. A likely explanation for these discrepant findings is the debate over the best method of expressing salivary IgA changes during exercise. Raw IgA concentrations do not account for changes in saliva composition typically associated with exercise (CHICHARRO et al, 1998). IgA:Protein has been the traditional method to correct for the drying effects of exercise on oral surfaces (REID et al, 2001). However, exercise typically produces an increase in the total protein content of saliva, thus apparent decreases in salivary IgA:Protein following exercise may reflect changes in the total protein content of the saliva sample, rather than fluctuations in IgA (REID et al, 2001).

### **Mechanisms behind the immune response to exercise**

#### *Cortisol and Catecholamines*

Cortisol has been related to many of the immunosuppressive and cell trafficking changes experienced during recovery from long endurance exercise (SHINKAI et al, 1996). Glucocorticoids administered in vivo have been reported to cause neutrophilia, eosinopenia, lymphopenia, and suppression of NK and T cell function, all of which occur during recovery from prolonged, high-intensity aerobic exercise (CRUPPS & FAUCI, 1982).

Immediately following a long, intense bout of aerobic exercise, plasma catecholamines are elevated. Epinephrine and norepinephrine play an important role in recruiting lymphocytes to the circulation. Epinephrine infusion induces changes in immunity similar to those induced by heavy endurance exercise including NK cell activity (KAPPEL et al, 1991), mitogen-induced lymphocyte proliferation (TVEDE et al, 1994), increases in IL-6 (STEENBERG et al, 2001), and is also associated with lymphocyte apoptosis (JOSEFSSON et al, 1996).

However, epinephrine and norepinephrine's effects are lessened after intensive exercise of >90 min duration (NIEMAN, 1997). Immediately after exercise of 2.5-3 h duration, the lymphocyte count is virtually unchanged from resting values (NIEMAN et al, 1995b). This contrasts sharply from the marked increase in lymphocyte count that is measured after exercise of <90 min duration (NIEMAN, 1995; PEDERSON et al, 1997). Thus, the hormonal milieu following prolonged endurance exercise >90 min appears to favor cortisol- rather than catecholamine-mediated effects (NIEMAN, 1997).

In contrast, several studies (CARLSON et al, 2008; KOCH et al, 2001; NIEMAN et al, 2004) of the immune response to resistance exercise have failed to establish any connection between cortisol and measured exercise-evoked perturbations in immunity. Thus it appears unlikely that post-exercise increases in cortisol play a clinically significant role in any resistance exercise-induced alterations in immune function.

The rise in the epinephrine and norepinephrine following resistance exercise has been less extensively studied. Nieman et al. (1005a), directly measured epinephrine and norepinephrine concurrent with measures of immune function following resistance exercise. They reported that, while norepinephrine levels rose substantially (>400% above



resting) epinephrine concentrations after sets of exhaustive resistance exercise rose only modestly (0.77 nmol/l), and were closer to those observed after treadmill walking at 50%  $VO_{2max}$  (0.568 nmol/l) than those measured after running at 80%  $VO_{2max}$  (1.29nmol/l). Heavy resistance exercise strongly activates the sympathetic nervous system. The sympathetic nervous system is strongly linked to immune function, with innate immune cells expressing both alpha- and beta-adrenergic receptors and T-cytotoxic and B-lymphocytes expressing beta2-adrenoreceptors (NANCE e SANDERS, 2004). Given the lack of findings regarding a cortisol effect, the hormonal milieu after resistance exercise appears to favor sympathetic nervous activation rather than cortisol-mediated effects.

### *Muscle Damage*

Exercise, particularly eccentric muscle actions, can induce significant microtrauma to muscle fibers. When mechanical forces placed upon the myofiber exceed the structural capacity of the membrane, microtears in the sarcolemma occur. Consequently, intramuscular components, such as enzymes, leak out of the damaged muscle fiber and into circulation. Serum concentrations of the muscle enzyme creatine kinase (CK) have been used as indicators of muscle damage following resistance exercise and may indicate the status of the muscle cell membranes. Tissue damage leads to activation of the immune system. The overall response is characterized by a movement of fluid, plasma proteins and immune cells from the circulation to the injured tissue. Neutrophils and monocytes are the primary immune cell types involved in this process. Their actions are coordinated to a large degree by cytokines (SIMPSON et al, 1997).

The extent of muscle damage appears to impact the acute immune response chiefly in regards to circulating cytokine levels. Muscle damage-inducing (as measured by CK concentrations) eccentric cycling exercise yielded greater increases in plasma IL-6 than a concentric-only bout, despite a matching metabolic and hormonal demand between the two. Additionally, the increases in IL-6 were correlated to increases in CK (BRUUNSGAARD et al, 1997). Also, increases in IL-6 2h after resistance exercise are related to the extent of DOMS reported 24 h after exercise (MACINTYRE et al 2001). Relative to strenuous endurance exercise, eccentric-only resistance exercise (4 sets of 12 repetitions of leg curl and bench press) induced a smaller rise in cytokines, which occurred later after the termination of exercise (SMITH et al, 2000). However, any substantial rise in cytokines may be clinically meaningful.

From a clinical standpoint, the relationship between exercise-induced skeletal muscle microtrauma and the production of cytokines might be the most relevant immune response to exercise. Smith (2000) has proposed a model implicating cytokines as the key effectors behind the physiological symptoms associated with the overtraining syndrome. According to her theory, overtraining occurs if local inflammation, induced by acute exercise, is not resolved before subsequent bouts of exercise are performed. If insufficient recovery is given before subsequent bouts of exercise are performed, the local inflammation can become chronic local inflammation, and eventually, chronic systemic inflammation. With chronic systemic inflammation, monocytes become activated to release large quantities of proinflammatory cytokines. In particular, the pro-inflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 are implicated as central to this theory of overtraining. IL-1 $\beta$  and TNF- $\alpha$  are secreted at the onset of inflammation, and they act systemically on the liver to induce acute phase protein synthesis, the hypothalamus to change the body temperature set-point, assisting in the control of fever, and higher centers of the brain. IL-6 displays both pro-inflammatory (mediating the acute phase response) and anti-inflammatory effects (synthesis of glucocorticoids). Chronically-elevated levels of these cytokines can induce "sickness" behavior, characterized by a loss of appetite, weight loss, sleep disturbances, depression,

etc. (HART, 1988), via direct activation of the central nervous system (BIFFL et al, 1996). Further, cytokines would increase glycogen and acute protein synthesis in the liver, activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, altering blood levels of catecholamines, glucocorticoids, and gonadal hormones. Immune suppression would possibly result as well, as a consequence of the anti-inflammatory factors released in conjunction with the pro-inflammatory response to tissue trauma (SMITH et al, 2000).

### **Influence of Training Status**

The most effective way to ameliorate any potentially immunosuppressive effects of exercise on immune function appears to be engaging in a regular training program. After the first exposure to eccentric exercise, subjects typically display substantial evidence of microtrauma. Upon a second exposure to the same exercise stimulus, markers of inflammation and muscle damage are often markedly reduced. This phenomenon is termed “the repeated bout effect”. The repeated bout effect is a well-documented illustration of an organism’s adaptation to exercise stress. Documentation of the repeated-bout effect includes a lower pro-inflammatory cytokine profile (SMITH et al, 2007) and lower post-exercise neutrophilia (PIZZA et al, 2001) following a second exposure to the same exercise stimulus. Adaptations behind the repeated bout effect are thought to include a shift towards greater recruitment of slow-twitch motor units and the generation of new sarcomeres in series, thereby reducing the extent of microtrauma, and a downregulation of inflammation, that would limit the extent of post-exercise cell damage in the days following the exercise (MCHUGH, 2003).

In cross-sectional comparisons, trained subjects show less evidence of tissue trauma following the same exercise stimulus than untrained subjects. For example, Newton et al. (2008) found smaller fluctuations in plasma CK activity and arm circumference, and a quicker recovery of strength in trained than untrained subjects following 10 sets of six maximal voluntary eccentric elbow flexions (NEWTON et al, 2008). Markers of oxidative stress following sprinting or weightlifting exercises were found to be lower in anaerobically trained athletes than those previously reported in untrained individuals (BLOOMER et al, 2006). Mooren et al. (2004) observed that athletes with a high  $VO_{2max}$  ( $\geq 60 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; assumed to be more highly trained) had no increase in apoptotic lymphocytes following a marathon, while less well-trained athletes ( $VO_{2max} \leq 55 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) experienced substantially elevated lymphocyte apoptosis above resting levels. Thus the lymphocytes of well-trained aerobic athletes appear to be more resistant to exercise-induced apoptosis.

Potteiger et al. (2001) found trained women displayed no reduction in PHA-stimulated lymphocyte proliferation following a whole-body resistance exercise routine, while a significant reduction in lymphocyte proliferation was noted for untrained women who exercised at the same relative intensity (POTTEIGER et al, 2001). In contrast, Dohi et al. (2001) found lower B-cell proliferation after six sets of squat at RM loads in better-trained subjects (DOHI et al, 2001) than in those who were less well-trained. A likely reason for these discrepant findings is that subjects in Dohi’s study exercised to their repetition maximum on each set, and the better-trained subjects were working at a higher absolute intensity - as evidenced by a trend towards greater cortisol release in the trained group (DOHI et al, 2001). Thus it appears that training potentially ameliorates post-exercise fluctuations in immunity – when compared to an exercise stimulus of the same absolute, submaximal workload.

While it may attenuate the immune response to acute exercise, regular training does not appear to greatly impact resting measures of immunity. Most measures of resting immune function show little or no difference between athletes and untrained controls



(MACKINNON, 2000).

### **Clinical Relevance of Immune Response to Resistance Exercise**

The Acute changes in immunity following heavy exercise (including resistance exercise) are typically looked on as potentially markers of a transient immunosuppression. This has led to the formulation of the "Open-Window" theory of immunosuppression, which proposes that athletes who train rigorously, repeatedly induce a short-term down-regulation of immunosurveillance. As a consequence, foreign pathogens are given a foothold to infect the host.

Acceptance of the open-window theory is tempting, and is bolstered by the availability of epidemiological data showing that hard-training athletes do report more sicknesses than sedentary controls. However, as Nieman has pointed out (NIEMAN, 1997), no one has yet linked the transient alterations in immunity after heavy exercise with an increased risk of sickness. Until that correlation is made, the Open-window theory is still subject to challenge.

Regular training attenuates the immune response to resistance exercise. Care should be taken to ensure that resistance training is planned, with adequate variation in intensity and volume over time to ensure recovery and avoid chronic systemic inflammation.

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