# *Spinal cord injury: Known and possible influences on the immune response to exercise*

**Leicht, C.A.[1], Goosey-Tolfrey V.L.[1] and Bishop, N.C.[1]**

[1] School of Sport, Exercise and Health Sciences; The Peter Harrison Centre for Disability Sport, Loughborough University, Leicestershire, UK.

## TABLE OF CONTENTS


15800

*Direct correspondence to:* Dr Nicolette C. Bishop, PhD, School of Sport, Exercise and Health Sciences, The Peter Harrison Centre for Disability Sport, Loughborough University, Loughborough, Leicestershire, LE11 3TU, England, UK, Tel: +44 (0) 1509 226385, E-mail: n.c.bishop@lboro.ac.uk

## ABSTRACT

A spinal cord injury (SCI) can increase the risk of infection by impacting on many aspects of immune function; one particularly well-documented observation is a reduction in lymphocyte numbers. The vast majority of lymphoid cells express adrenergic receptors. Therefore, autonomic function loss and concomitant alterations in resting and post-exercise catecholamine concentrations, particularly so in individuals with a tetraplegia, may impact directly on immune cells and depress immunity. Other factors are further likely to contribute, examples including altered muscular, endocrine and cardiovascular function following SCI. However, some alterations, such as increases in natural killer cell cytotoxicity following exercise in those with a tetraplegia, are unrelated to the catecholamine response. Likewise, mucosal immunity in individuals with a tetraplegia appears to be similarly influenced by exercise as in the able-bodied population. Indeed, rehabilitation therapy and exercise can increase some measures of immunity and autonomic function in those with an SCI. It is therefore possible that compensatory mechanisms offset disability-related detriments. This may be by way of sympathetic reflex activity, receptor hypersensitivity, or parasympathetic and neuroendocrine adjustments. Future work needs to explore these mechanisms further to clarify the implications of an SCI on the immune response to exercise and susceptibility to infection.

In this article, we review the impacts of an SCI on immune, and specifically, exercise immune function. The relevant anatomical and physiological foundations of the immune system are first briefly laid out in order to understand the potential impacts of neural and neuroendocrine dysfunction on the immune system. With the limited number of human studies available, we have then aimed specifically to gather all relevant existing literature on exercise immunology in individuals with an SCI in patient, recreationally active and athlete populations. We believe that an understanding of the impacts of exercise can provide a tool to help maintain or improve health in individuals with an SCI.

A comprehensive literature search was conducted using the search engines PubMed, SPORTDiscus, Web of Science and Zetoc, search period June 2012 – February 2013. Key words employed included spinal cord injury, immunology, exercise, paraplegic, tetraplegic, upper body exercise, interleukin, immunoglobulin, sympathetic, and parasympathetic. All articles and articles derived from their reference lists were checked for their suitability.


**Key words:** Catecholamines, cytokines, natural killer cells, autonomic nervous system, mucosal immunity

## 1 INTRODUCTION

An SCI increases the risk of infection, and complications from infection are among the leading causes of re-hospitalization and death in the post-acute phase

following SCI (12, 76). Specifically, pneumonia, influenza, or other respiratory complications accounted for the majority of deaths in a large scale study conducted on 886 individuals with SCI between 1943 and 1990 (22). Heightened infection and illness susceptibility are acknowledged sequelae of acute, subacute and chronic SCI that challenge the activity, satisfaction, productivity, and health of its survivors (59). Apart from the deleterious consequences for the suffering individual, there are economic consequences and strain on health care providers.

Therapeutic exercise for individuals with SCI is actively encouraged and interest in wheelchair sports is increasing, particularly with the legacy of the London 2012 Paralympic Games. The advancements in wheelchair design (1), combined with greater funding opportunities and sports professionalism have resulted in a greater number of wheelchair athletes performing on recreational (36) and professional levels (31); likewise, the quality of the sports performance has improved. This is supported by analysis of objective markers of physical performance by both sports scientists and coaching support staff, which, when investigating peak oxygen uptake as an example, has increased around two-fold within 30 years (32, 38).

The able-bodied literature reports a higher prevalence of symptoms of respiratory illness in athletic than non-athletic populations, with a marked number of these infectious in nature (16, 77), which underlines the practical importance to analyse immune function in athletes with an SCI. Understanding the influence of exercise on immune functions is potentially critical for the management of infections in individuals with SCI, given the substantial impacts of exercise on immune functions (87). Furthermore, from a mechanistic point of view, SCI provides exercise immunologists with an ideal *in vivo* model with which to investigate the influences of the autonomic nervous system on the immune response to exercise.

## 2 PHYSIOLOGICAL BACKGROUND: COMMUNICATION BETWEEN THE IMMUNE SYSTEM AND THE BRAIN

### 2.1 Role of the autonomic nervous system

The central nervous system receives messages from the immune system and, vice versa, messages from the brain modulate immune functions (21). Some of these unconscious actions are modulated by the autonomic nervous system. Moynihan *et al.* (57) and Elenkov *et al.* (21) summarize three lines of evidence supporting sympathetic nervous system (SNS) involvement in immune regulation:

1. Lymphoid organs are innervated by sympathetic noradrenergic nerve fibres.
2. The vast majority of lymphoid cells express adrenergic receptors.
3. Noradrenaline, an important neurotransmitter of sympathetic nerves, is released in lymphoid organs following immunization.

The rapid, "real-time" brain control of innate immune mechanisms underlying inflammation is thought to be based on autonomic neuronal projections to sites of inflammation (65). Evidence accumulated in the last decades indicates that,

peripherally, both noradrenaline released from the non-synaptic sympathetic nerve terminals and adrenaline (and to a lesser extent, noradrenaline) released from the adrenal medulla are involved in immunomodulation (21), resulting in both activation and suppression of immune parameters (Table 1).

Table 1: Evidence of catecholamine action on immune cells.

| **References** | **Findings** |
|---|---|
| Kappel *et al.*, 1991; Tonnesen *et al.*, 1987 | Natural killer cell activity is increased following both infusion of adrenaline and exercise, which naturally increases catecholamine concentration. |
| Keller *et al.*, 1983 | Stress-induced lymphopenia is adrenal-dependent: adrenaline correlates inversely with lymphocyte number, as shown in animal stress experiments (stressor: electrical shocks). |
| Landmann *et al.*, 1984 | Even moderate physical stress (15 min, increasing up to 75% of maximum power output) results in an increase of adrenaline, which correlates negatively with the $T_{helper}/T_{suppressor}$ cell ratio. These authors suggest that adrenaline plays a role in the mobilisation of immunocompetent cells and may lead to a distribution pattern favouring immunosuppression during stress. |
| Nash, 1994 | Adrenaline administration causes a transitory leuko- and moncytosis. Sympathectomy can lead to decreases in natural killer cell cytotoxicity, and reduce the $T_{cytolytic}/T_{suppressor}$ cell ratio and B cell numbers. |
| McHale & Thornbury, 1990 | Sympathetic nerve stimulation increases lymphocyte output in anaesthetised sheep. |

In addition to the sympathetic strand of the autonomic nervous system, efferent fibres of the vagus nerves are involved in immune responses. For example, they inhibit the release of pro-inflammatory cytokines and regulate inflammation, coining the term cholinergic anti-inflammatory pathway (65). Experimentally, peripheral vagus nerve stimulation in vagotomized rats prevents the development of acute inflammation (6). The importance of intact innervation on immune control is also evident in humans, as denervated skin has a greatly reduced leukocyte infiltration following local damage, which is associated with a ~70% reduction in the rate of wound healing compared with normal skin (20). In chronic SCI, it has further been suggested that those with low fibronectin levels may present impaired wound healing, whilst lower zinc levels have been found in those presenting pressure ulcers (17).

Salivary glands are involved in the defence of the mucosa, and salivary secretory immunoglobulin A (SIgA) is the predominant immunoglobulin in saliva. It plays an important role in mucosal immunity and has therefore been described as “first line of defence” against pathogens and antigens presented at the mucosa, such as cold-causing viruses (4, 87). In analogy to immune cells as described above, salivary glands are innervated by autonomic nerve fibres. These originate from the upper thoracic segments, although it remains unclear precisely where in this region (69). In rats, sympathectomy results in a decreased SIgA secretion (70). Conversely, both parasympathetic and sympathetic stimulation of rat salivary glands can increase salivary gland blood flow, saliva flow rate, and SIgA secretion (13, 14, 69). Similarly, infusion of sympathetic and parasympathetic agonists can increase SIgA secretion rate (71).

The autonomic nervous system is not only involved in the execution of immune responses, but has also a sensory component. Afferent vagus nerve fibres rapidly signal the brain to trigger immunomodulatory responses in the early phases of inflammation (65). Peripheral sensory nerves are further part of reflex pathways to contribute to proinflammatory function, which includes vasodilation and mast cell activation (20). These reflex pathways consist of sensory receptors, afferent pathways, integration centers in the central nervous system, efferent pathways, and effector organs (29). Reflex pathways may also be activated by causes other than injury or inflammation; for example, they are involved during static muscle contraction, which increases adrenal sympathetic nerve activity in rats (86).

### 2.2 Role of humoral factors

In addition to the neural pathways, humoral factors are involved in the communication between the brain and the immune system. One pathway that has been explored extensively is the hypothalamus-pituitary-adrenal (HPA) axis, where adrenocorticotropic hormone (ACTH) released from the pituitary stimulates glucocorticoid secretion in the adrenal gland (30, 65). One of the most prominent glucocorticoids is cortisol, with generally immunosuppressive and anti-inflammatory effects (21). Importantly, humoral feedback mechanisms can inform the brain on immunologic actions in the body, and hence, modify its behaviour. For example, cytokines and other soluble factors secreted in response to infection or inflammation (such as the tumour necrosis factor, TNF-$\alpha$), produced by immune cells, do not only attract and modulate other immune cells locally, but can act on sensory neurons or the brain directly. In the context of this review, it is important to note that not only immune cells can trigger a cascade of immune actions, also cytokines released by working muscle (myokines) in response to exercise are capable of triggering an immunologic response (67).

## 3 SPINAL CORD INJURY: IMPACTS ON AUTONOMIC FUNCTION

As outlined above, an important route of communication between the brain and the immune system is via autonomic pathways descending the spinal cord. Given that sympathetic neurons exit the spinal cord at the thoracic (T) and high lumbar (L) level (T1-L2) (29, 49), a complete SCI at the T level (resulting in paraplegia) partly interrupts sympathetic pathways, while a complete cervical SCI (resulting in tetraplegia) completely abolishes sympathetic communication between brain and effector cells/organs (Fig. 1). Autopsy findings in patients with cervical SCI show a marked loss of axons in the dorsal aspects of the lateral funiculus, which is thought to be the location of the descending vasomotor pathways (29). Only injuries below L1 have minimal effects of SNS dysregulation (29). Hence, sympathetically governed function is impaired in individuals with a tetraplegia (TETRA), and one obvious observation in a sporting context includes the reduced maximum heart rate, which is in the range of around 130 beats per minute in these individuals (3). Spinal segments T2 to T4 supply sweat glands of the head and neck, T2 to T8 of the upper limbs, T6 to T10 of the trunk, and T11 to L2 of the lower extremities (29), explaining the reduced ability to sweat in TETRA. Fur-

ther, basal systolic and diastolic blood pressure in TETRA is about 15 mm Hg lower than that in able-bodied subjects (29). This accompanies the loss of motor and sensory control below the level of lesion. These adaptations lead to reductions in peak oxygen uptake in TETRA, even though the fittest individuals with a complete tetraplegia still reach scores of over 30 $mL \cdot kg^{-1} \cdot min^{-1}$ (51).

There is also evidence for an altered HPA axis function in SCI. Animal experiments show that an SCI acutely activates the HPA axis in mice, resulting in elevated circulating cortisol levels, even though cortisol returns to baseline values by 3 days post injury (54). It has been suggested that the acute trauma-induced activation of the HPA axis and the SNS (resulting in increased noradrenaline) axis helps prevent pathological autoimmune reactions, or prevents hyperactivation of

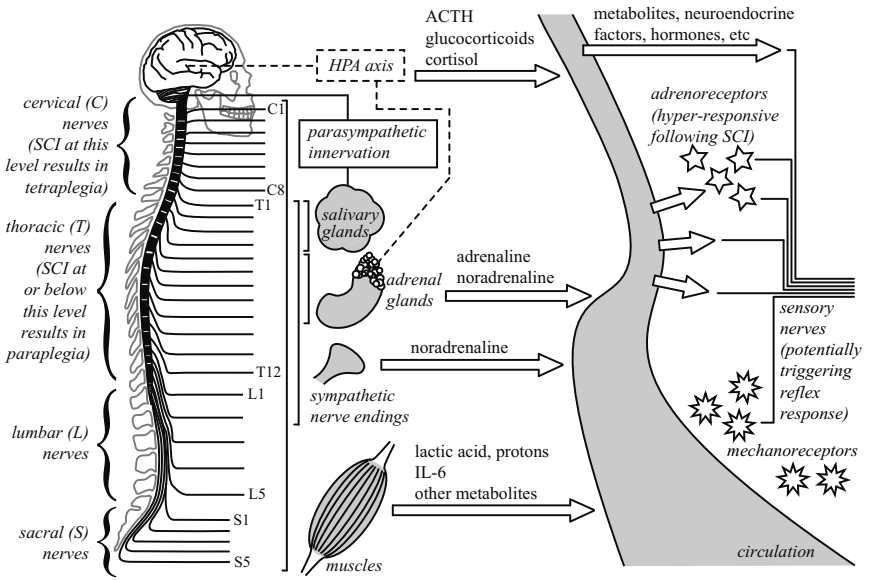


Figure 1: Anatomical and physiological basis for immunomodulatory processes potentially influenced by a spinal cord injury and/or exercise. For glands, sympathetic nerve endings and muscles, the origin of their nerves is shown. ACTH, adrenocorticotropic hormone; HPA, hypothalamus pituary adrenal; IL-6, immunoglobulin-6; SCI, spinal cord injury.

the immune system (55). In chronic SCI, a number of studies in humans document an altered pattern of markers of the HPA axis (8, 37, 48, 89), discussed in detail in section 4.1.

## 4 SPINAL CORD INJURY: IMMUNE FUNCTION AND THE IMPACTS OF EXERCISE

The section above shows that individuals with an SCI present altered autonomic control due to a dysfunctional SNS and, potentially, an altered HPA axis, two sys-

tems which are known to regulate immune responses. It is therefore legitimate to assume that this is one of the reasons for the increased infection risk in SCI and has led researchers to measure markers of immune function, the autonomic nervous system and/or the HPA axis in a range of contexts. Immune responses have initially been investigated in resting conditions in individuals with an SCI. However, the amount of research on exercise immune function has grown steadily in recent years, not least as the association between resting immune dysfunction and low levels of fitness in persons without SCI (60) implies a negative influence of a sedentary lifestyle. Consequently, exercise has been suggested already two decades ago to be one intervention to reverse the negative immune alterations in TETRA (11).

### 4.1 Cortisol

#### 4.1.1 Resting responses

Even though adaptations after an SCI include an increase in cortisol immediately after injury, urinary free cortisol concentration falls in normal range after 6 months post injury (17, 46). Kliesch et al. (46) further found a positive association between ACTH and cortisol in TETRA and in individuals with a paraplegia (PARA), indicating the normal function of the HPA axis despite an SCI. This work confirms the endocrine nature of ACTH action on cortisol secretion without the need of "hard-wired" neuronal mechanisms. Other researchers found a normal circadian rhythm of plasma cortisol concentration in TETRA, which further supports the concept of normal HPA axis function in this population (90).

However, there is evidence of a disturbed HPA axis following SCI, as indicated by elevated resting plasma cortisol levels in TETRA and PARA when compared with able-bodied controls, despite no differences in plasma ACTH (8). An impaired cortisol response to a corticotropin-releasing hormone (CRH) bolus in TETRA and PARA has further been observed (37). It must be noted, though, that this external CRH administration may cause a different response when compared with physiological changes of influencing metabolites, as, for example, found following exercise. The researchers of this project indeed point out that non-CRH or non-ACTH-dependent pathways may exist and compensate for their suggested HPA axis dysfunction in patients with an SCI (37).

#### 4.1.2 Exercise responses

The plasma cortisol concentration in athletic TETRA is increased following strenuous exercise, such as simulated race conditions (88). Some studies suggest a minimal exercise duration required for cortisol concentration to change. A full marathon (26) increases plasma cortisol concentration in PARA, whereas a half-marathon does not alter plasma cortisol levels in either TETRA and PARA (2, 27). However, this contrasts other reports where increases in cortisol have been observed after exercise durations as little as 20 minutes (15, 48). The similar rise in plasma cortisol following exercise between TETRA and able-bodied controls (15, 48) further support the concept that cortisol is mainly governed by the HPA axis, with no or only little contribution of the SNS. It has also been suggested that the myokine interleukin-6 (IL-6) may give rise to increased cortisol production

(30), as documented by plasma cortisol rises following IL-6 infusion (62, 79). It has been proposed that this may be by way of secretion modulation via a neuroendocrine-immune loop involving the HPA axis (68). However, IL-6 does not seem to be the main modulator of cortisol: Brief acute exercise increases plasma cortisol in TETRA, PARA and non-spinal cord injured individuals, yet IL-6 levels only increase in PARA and non-spinal cord injured individuals, but not in TETRA (64).

Recently, it has been suggested that one of the benefits of exercise is the creation of an anti-inflammatory environment (30). As exercise gives rise to a range of anti-inflammatory cytokines, it can reduce the "reactivity" of immune cells, for example by downregulating TOLL-like receptor expression on immune cells. Exercise can also reduce fat mass, itself a producer of inflammatory agents (30). Cortisol, with its potent anti-inflammatory effects, has been shown to remain elevated for longer following exercise in TETRA when compared with able-bodied controls (48, 89) thus creating an anti-inflammatory environment for a longer duration. Again, this may be because of secretion modulation via a neuroendocrine-immune loop involving the HPA axis (68), which may be altered in TETRA.

**4.2 Catecholamines**

Sympathetic neurons exit the spinal cord between T1 and L2 (29, 49), and the majority of sympathetic neurons innervating the adrenal medulla originate from T5-T9 (29). Unsurprisingly, due to the abolition of neural pathways to the adrenal gland and dysfunction of sympathetic pathways, catecholamine release is therefore affected in individuals with a high-level SCI.

Resting plasma catecholamine concentrations are lower in TETRA when compared with able-bodied individuals and controls with a low paraplegia, and the exercise-induced increase is smaller in TETRA (47, 73, 74) or not present at all (48, 89). Plasma adrenaline and noradrenaline remain unchanged in TETRA following simulated racing conditions (88) and graded exercise tests to exhaustion (23, 64, 88), and plasma adrenaline following a half marathon does not increase in TETRA, whereas it does increase in individuals with T4-L1 lesions (2). Individuals with a lesion in the T1-T6 area present a reduced catecholamine response to a graded exercise test to exhaustion when compared to those with a T7-T12 lesion (81). Serum noradrenaline is significantly elevated after exercise in both these groups, whereas adrenaline is only elevated in the T7-T12 group (81), underpinning the physiological relevance of intact adrenal gland innervation.

It is worth noting that in contrast to volitional exercise, exercise-induced increases in adrenaline and noradrenaline have been observed in both TETRA and PARA when electrically stimulating paralysed muscles, even though the relative increase to resting levels was lower than in able-bodied individuals (5). Spinal reflexes have been thought earlier to be the potential candidate for these catecholamine responses (5, 74). It therefore appears that despite the central abolition of neural pathways, ways remain to exert responses normally centrally governed by the SNS. Exploring methods to exert catecholamine responses in those with an impaired SNS could hence be a promising way to modulate and improve immune

function in this population. Catecholamines are known to exhibit both immunodepressive and -stimulating characteristics (Table 1). However, Nash (60) suggests that periods of autonomic dysreflexia in SCI with the concomitant catecholamine boost and spikes in circulating glucocorticoids may be primarily immunodepressive, creating a "window of opportunity" in which opportunistic infections ensue. It has been suggested that suppressed immune function following autonomic dysreflexia (due to lymphocyte apoptosis) may explain why individuals with high level SCI are at high risk for recurrent infections throughout their lifetime (55). Indeed, a number of articles compiled by Nash (60) show the relationship between repeated catecholamine overstimulation and depression of immune function. Nash (60) further points out that adrenergic stress in experimental animals suppresses lymphocyte mitogen proliferation and natural killer cell (NK) and phagocytic activity and diminishes interferon producing capacity, a pattern of immune irregularities nearly matching that of humans with SCI.

Table 2: Adaptations of cellular immunity following an SCI and effect of level of injury

| References | Findings |
|---|---|
| Campagnolo *et al.*, 2000; Cruse *et al.*, 2000; Kliesch *et al.*, 1996 | PARA below the T10 level exhibit normal NK cell cytotoxicity. It has hence been suggested that the effects of adrenal hormones and neurotransmitters on NK cell function represent critical targets for future investigation (17). Likewise, neutrophil phagocytic function is decreased in TETRA but not in PARA below the T10 level (9). |
| Campagnolo *et al.*, 1994; Campagnolo *et al.*, 2000 | Despite depressed NK cell levels in SCI, no difference in leucocyte counts, but increases in T and $T_{helper}$ cells in SCI. |
| Campagnolo *et al.*, 1994 | Depressed lymphocyte proliferative response in TETRA when compared to AB controls. |
| Held *et al.*, 2010 | Increased susceptibility to a virus load and reduced macrophage activation and virus-specific T cells that control virus replication in animal SCI models. |
| Ibarra *et al.*, 2007 | The T cell response to mitogen and antibody titre to antigen is reduced in animals with a chronic SCI (both at the T1 and T12 level). The immunosuppressive effect on both T cell and antibody reactions is stronger and lasts longer in the case of high (T1 level) and severe contusions, which gives rise to a higher risk to develop infectious diseases. |
| Iversen et al., 2000 | Reduced immunoglobulin G levels in TETRA and PARA when compared to AB controls. |

AB, able-bodied; NK, natural killer cell; PARA, individuals with a paraplegia; SCI, spinal cord injury; T, thoracic; TETRA, individuals with a tetraplegia.

## 4.3 Leukocytes

### 4.3.1 Resting responses

Animal experiments show that an SCI at the T3 level acutely reduces the antigen-specific immunoglobulin following vaccination, and reduces spleen weight, dendritic, B, and T cell numbers (54). In humans, a reduced NK count has been

reported in both TETRA (89) and PARA (60, 84). It has been proposed that the NK number depression in TETRA is due to a production problem in normally sympathetically innervated bone marrow (10). NK cytotoxicity can also show reductions in SCI, especially in high level SCI (above T6, affecting autonomic innervation), with NK cytotoxicity in TETRA being about 40-60% of normal (9-11, 40, 46, 61). Further dysfunction in SCI has been reported for a variety of other resting immune measures (Table 2).

**4.3.2 Exercise responses**

It seems that exercise does not destroy NKs; rather, they are temporarily relocated to reservoir sites such as the walls of peripheral veins in response to the exercise-induced secretion of catecholamines (87) - the concomitant downmodulation of adhesion molecules releases them into the circulation (58). Since individuals with a high level SCI have an impaired sympatheticoadrenal activity, with lower catecholamine concentrations measured at rest and following exercise, these studies support the concept that catecholamines are responsible for recruitment of leukocytes to the circulation at rest and during exercise. Depressed leukocyte number elevation has also been demonstrated in persons without disability who exercise under beta-adrenergic blockade, underpinning this suggestion (78).

NK number and cytotoxicity and other aspects of immunity are influenced by acute exercise of various intensities and durations, and numerous studies have shown a depressed response in TETRA (Table 3). However, it has been shown early that rehabilitation therapy, including strength, endurance and mobility training, improves NK cytotoxicity in patient TETRA and PARA, whereas NK cytotoxicity stays at a low level in those not receiving therapy (46). Interestingly, increases in NK cytotoxicity in TETRA are unrelated to changes in NK number (2, 47, 89). Mechanisms other than catecholamine activation must be considered as responsible, as for example, NK cytotoxicity in both PARA and TETRA is elevated after a half-marathon despite no increases in adrenaline (2). It is hence possible that the altered, elevated cortisol response in TETRA (48, 89) modulates leukocyte function following exercise.

**4.4 Cytokines**

Appreciable numbers of individuals with SCI have abnormally high levels of pro-inflammatory cytokines whether or not they are symptomatic for infection. It is not surprising that these pro-inflammatory markers are further elevated in those with medical complications, such as urinary tract infection or pressure ulcers (18). Specifically, elevated plasma IL-6 concentrations and elevated soluble IL-2 receptor concentrations have been reported (60). Importantly, plasma IL-6 concentrations are related to reduced pulmonary function in SCI (28) and therefore may have some predictive power of health measures.

However, the manner of the acute cytokine response to strenuous exercise appears again to be lesion level dependent. Plasma IL-6 concentrations have been shown to increase in response to 20 minutes of upper body exercise (48) or a test to exhaustion (64) in PARA and AB, whereas it remains unaffected in TETRA (48, 64). It must be noted that IL-6 production is dependent on the duration of exer-

Table 3: Acute exercise effects on leukocyte number and activity in individuals with a spinal cord injury. Reported changes compare pre exercise with immediately after exercise values.

| References | N | Impairment | Activity level | Exercise intervention | Immune measure | Change in immune measure |
|---|---|---|---|---|---|---|
| Banno *et al.*, 2012 | 6 | TETRA (C6-C8) | recreational athletes | half marathon | NK cell number and cytotoxicity | number: no change (TETRA), 1.7-fold increase (PARA); cytotoxicity: 1.3-fold increase in both groups |
| | 7 | PARA (T5-L4) | recreational athletes | | lymphocyte number | no change |
| | | | | | leukocyte number | 1.8-fold increase in both groups |
| Furusawa *et al.*, 2003 | 7 | PARA (T7-L1) | recreational athletes | half marathon | NK cell number and cytotoxicity | number: no change, cytotoxicity: 1.2-fold increase |
| | | | | | lymphocyte number | no change |
| | | | | | leukocyte number | 2-fold increase |
| Furusawa *et al.*, 1998 | 9 | PARA (T5-T12) | elite athletes | marathon | NK cell number and cytotoxicity | number: 2.4-fold decrease, cytotoxicity: 1.1-fold decrease |
| | | | | | lymphocyte number | no change |
| | | | | | leukocyte number | 2.5-fold increase |
| Kawashima *et al.*, 2004 | 10 | PARA (T5-T12) | patients | 20 min orthotic gait exercise | NK cell number and cytotoxicity | number: no change, cytotoxicity: 1.4-fold increase |
| Klokker *et al.*, 1998 | 6 | TETRA (C5-C7) | participating in on-going training programme | 30 min functional electrical stimulation (maximal tolerable load for this duration) | NK cell number and cytotoxicity | number: no change (TETRA), 2-fold increase (PARA); cytotoxicity: increase in both groups (extent not stated) |
| | 5 | PARA (T4-T7) | | | lymphocyte number | increase in both groups (extent not stated) |
| | | | | | leukocyte number | increase in both groups (extent not stated) |
| Kouda *et al.*, 2011 | 8 | TETRA (C6-C7) | regularly active | 20 min arm cranking at 60% $\dot{V}O_{2max}$ | lymphocyte number | no change (TETRA), 1.3-fold increase (AB) |
| | | | | | leukocyte number | no change (TETRA), 1.5-fold increase (AB) |
| | 8 | AB | not stated | | prostaglandin $E_2$ | 1.5-fold increase (TETRA), no change (AB) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nash, 1994 | 8 | TETRA (no details given) | not stated | functional electrical stimulation elevating $\dot{V}O_2$ five-fold (duration not stated) | NK cell number and cytotoxicity<br>lymphocyte and leukocyte numbers | number: 1.8-fold increase; cytotoxicity: 2.5-fold increase<br>no change |
| Ueta *et al.*, 2008 | 7 | PARA (T11-L4) | regularly active | 120 min arm cranking at 60% $\dot{V}O_{2max}$ | NK cell number and cytotoxicity | number: no change in both groups; cytotoxicity: 1.1-fold decrease (PARA), 1.2-fold increase (AB) |
| | 6 | AB | not stated | | lymphocyte number<br>leukocyte number<br>prostaglandin $E_2$ | 1.9-fold increase (PARA), no change (AB)<br>1.6-fold increase in both groups<br>6-fold change (PARA), no change (AB) |
| Yamanaka *et al.*, 2010 | 8 | TETRA (C6-C7) | regularly active | 20 min arm cranking at 60% $\dot{V}O_{2max}$ | NK cell number and cytotoxicity | number: no change (TETRA), 1.8-fold increase (AB); cytotoxicity: no change (TETRA), 1.4-fold increase (AB) |
| | 6 | AB | not stated | | lymphocyte number<br>leukocyte number | no change (TETRA), 1.4-fold increase (AB)<br>no change (TETRA), 1.3-fold increase (AB) |

AB, able-bodied; C, cervical; L, lumbar; NK, natural killer cell; PARA, individuals with a paraplegia; T, thoracic; TETRA, individuals with a tetraplegia.

cise, with longer lasting activities resulting in more pronounced IL-6 level increases (30). Further, the IL-6 response is sensitive to the exercise intensity, directly representing the muscle mass involved, which decreases the higher the SCI lesion level. Upper body exercise per se (and even more pronounced when performed by persons with high level SCI), may therefore be insufficient to increase IL-6 above resting levels (68). Additionally, the before mentioned dysfunction of autonomic innervation could impact on IL-6 appearance in the blood, as catecholamines have been shown to influence cytokine production (65). Indeed, infusion of catecholamines can partly explain some of the rise in plasma concentrations of IL-6 found following exercise (24, 80), and administration of adrenergic antagonists can block adrenaline-stimulated IL-6 expression (24). This supports our finding that the plasma IL-6 response to strenuous exercise is associated with that of plasma adrenaline; responses of both are impaired in TETRA, but not in PARA or AB (64). This is an important issue as several immune responses are mediated by cytokines. For example, IL-6 infusion (amounts corresponding to levels of strenuous exercise) results in acute increases in neutrophils, cortisol, IL-10 and IL-1 receptor antagonist in healthy able-bodied individuals (79). Taken together, the combination of autonomic dysfunction impacting on cytokine production and less active, cytokine producing, muscle mass are the most likely reasons for the depressed production of IL-6 in TETRA. Given the messenger actions of IL-6, depressed levels may then impact on the production of other

cytokines/messenger molecules or alter immune cell number and function directly. Furthermore, an impaired IL-6 response to exercise may have downstream influences on metabolic responses, given the known glucoregulatory functions of IL-6 (68).

### 4.5 Salivary markers and upper respiratory symptoms

Mucosal immune function and its modulation by exercise have only recently been investigated in the SCI population. SIgA has been analysed in a number of studies to document the impact of chronic (53) and acute (51, 52) exercise in athletes with SCI. It was found that whilst slight differences in the SIgA response to exercise between TETRA and the control groups (PARA and able-bodied) exist (52), the overall pattern of the SIgA response is comparable between these groups. It was therefore suggested that the impact of sympathetic dysfunction on SIgA secretion in TETRA may be compensated by mechanisms such as reflex activity, by the parasympathetic nervous system, or by hypersensitivity of receptors (51).

A reduced SIgA secretion rate during periods of heavy training (53) is consistent with the positive relationship between post-race self-reported upper respiratory tract infections and training volume in athletes with an SCI (25). Epidemiological data from a large scale (N=18,693) study reveal that despite upper respiratory tract infections being the most prevalent acute respiratory condition in SCI, the annual outpatient visit rate is only 68/1000 – surprisingly, a lower rate when compared with the general population (155/1000) (75). Another epidemiological study investigating both TETRA and PARA reports a higher importance of pulmonary function, history of illness and smoking for chest illness than level or completeness of injury (82). In the case of pulmonary function, this may suggest a parameter that is trainable and that training may therefore decrease the risk of illness – indeed, very low incidences of upper respiratory symptoms were reported in wheelchair rugby athletes with tetraplegia during an observational study, with only 3 out of 14 athletes presenting light symptoms over 5 months (53).

## 5 IMPACTS OF MUSCULAR, VASCULAR, AND PSYCHOLOGICAL CHANGES AFTER SPINAL CORD INJURY

Apart from SNS and HPA dysfunction, it should be acknowledged that other disability-related factors may impact on immune function and further contribute to heightened illness susceptibility. For example, the colony-forming potential of progenitor cells from the bone marrow is reduced in SCI, which may be explained by inactivity characterising these individuals, possibly impairing blood flow through decentralized bone marrow (40). However, as long term adaptations to SCI include reductions in muscle mass, vessel diameter and blood flow below the level of lesion (63), this suggestion may not be limited to inactive individuals with an SCI but concern the SCI community as a whole. Furthermore, lesion level dependent paralysis of respiratory muscles can reduce respiratory function and the ability to cough and clear secretions that arise from respiratory infections (7). Respiratory training can improve respiratory parameters in SCI, such as maximum inspiratory and/or expiratory strength, vital capacity and maximum volun-

tary ventilation (19, 33, 85). Due to an improved ability to clear secretions, this may potentially reduce the risk of secondary complications, especially in individuals with high lesion levels. Finally, psychological stress and depression have known depressive effects on immune function, most likely via autonomic nervous and neuroendocrine system modulation (11). Given the psychological effects of SCI, this is likely to contribute to immune alterations in this population.

## 6 POTENTIAL COMPENSATORY MECHANISMS AFTER SPINAL CORD INJURY

Compensation of function loss is an intriguing field in exercise immunology in SCI populations. For example, receptors can adapt to an SCI and become hyperresponsive, as confirmed by adrenaline and noradrenaline injection in sympathectomized rats (66). It has also been observed that following SCI, spinal circuits are capable of generating some sympathetic activity, and a peripheral α-adrenoreceptor hyper-responsiveness may help to maintain normal function despite depressed circulating levels of catecholamines (29). Further studies during anaesthesia document increases in catecholamines, ACTH, and cortisol following functional electrical stimulation of anaesthetized limbs (45), suggesting that spinal reflexes and humoral feedback can potently regulate immune responses during exercise. It has also been suggested that the blockade of IL-6 signalling after SCI in mice inhibits classic pathways and promotes an alternative pathway of macrophage activation (34). Likewise, the reported higher levels of dehydroepiandrosterone sulphate (which enhances IL-2 and has anti-glucocorticoid effects) in TETRA may be a compensatory response by the neurohormonal-immune axis to augment an injury-related impairment in the SNS or the immune response itself (8, 9) On a cellular level, increased fractions of T and $T_{helper}$ cells in TETRA and PARA may be a compensatory change related to reduced numbers of NKs (10). Other mechanisms that may compensate for loss of sympathetic function include serotonin (synthesis known to increase during exercise and influence T cells, macrophages and NKs), vasoactive intestinal peptide, substance P or neuropeptide Y, all known to have immunomodulatory capacity (41). Yet for many of these substances, the link between exercise and altered immune function in humans or indeed individuals with an SCI has not been studied in detail (41).

## 7 CONCLUSION

An SCI, particularly above the T6 level, impacts on immune function, partly caused by the dysfunction of sympathetic pathways and possibly an altered HPA axis. Reduced resting levels and depressed exercise responses of the end products of the SNS and a number of immune measures have consistently been found in TETRA. However, even though a number of studies report depressed immune measures or depressed levels of immunomodulatory substances in response to exercise in high level SCI, there is very little empirical (rather than anecdotal) evidence reporting illness rates in TETRA athletes. The impact of high level SCI on immune responses to exercise is likely to be influenced by the redundancy of the

bidirectional talk between central nervous and the immune system, which seems to be able to compensate some of the lost function. Compensatory mechanisms are likely to include reflex activity, receptor hypersensitivity, or parasympathetic and neuroendocrine adjustments. Future work should address the influence of time since injury on the impact of exercise on immune measures (and infection frequency) as such compensatory mechanisms will likely develop over a period of months, or even years. Further, as participation in wheelchair exercise involves all levels of activity, from the recently injured to the Paralympian, the effect of activity on immune functions and the immune response to exercise should be considered when investigating optimal exercise intensities for both health and performance in SCI. Future work may further investigate the possibility of lesion-level/impairment-dependent individual exercise prescription to help counteract depressed immune function following SCI. Finally, individuals with SCI may serve as experimental models to better understand the impact of various levels of lesion and therefore help elucidate the mechanisms underlying the immune response to exercise.

## Acknowledgements

We thank the Peter Harrison Centre for Disability Sport for on-going support. No other sources of funding were used to assist in the preparation of this review, and the authors declare no conflict of interest.

# 8 REFERENCES

1. Ardigo' LP, Goosey-Tolfrey VL and Minetti AE. Biomechanics and energetics of basketball wheelchairs evolution. Int.J.Sports Med. 26: 388-396, 2005.
2. Banno M, Nakamura T, Furusawa K, Ogawa T, Sasaki Y, Kouda K, Kawasaki T and Tajima F. Wheelchair half-marathon race increases natural killer cell activity in persons with cervical spinal cord injury. Spinal Cord 50: 533-537, 2012.
3. Bhambhani Y. Physiology of wheelchair racing in athletes with spinal cord injury. Sports Med. 32: 23-51, 2002.
4. Bishop NC and Gleeson M. Acute and chronic effects of exercise on markers of mucosal immunity. Front.Biosci. 14: 4444-4456, 2009.
5. Bloomfield SA, Jackson RD and Mysiw WJ. Catecholamine response to exercise and training in individuals with spinal cord injury. Med.Sci.Sports Exerc. 26: 1213-1219, 1994.
6. Borovikova LV, Ivanova S, Nardi D, Zhang M, Yang H, Ombrellino M and Tracey KJ. Role of vagus nerve signaling in CNI-1493-mediated suppression of acute inflammation. Auton.Neurosci. 85: 141-147, 2000.
7. Brown R, DiMarco AF, Hoit JD and Garshick E. Respiratory dysfunction and management in spinal cord injury. Respir.Care 51: 853-870, 2006.
8. Campagnolo DI, Bartlett JA, Chatterton R,Jr and Keller SE. Adrenal and pituitary hormone patterns after spinal cord injury. Am.J.Phys.Med.Rehabil. 78: 361-366, 1999.

9. Campagnolo DI, Bartlett JA and Keller SE. Influence of neurological level on immune function following spinal cord injury: a review. J.Spinal Cord Med. 23: 121-128, 2000.
10. Campagnolo DI, Dixon D, Schwartz J, Bartlett JA and Keller SE. Altered innate immunity following spinal cord injury. Spinal Cord 46: 477-481, 2008.
11. Campagnolo DI, Keller SE, DeLisa JA, Glick TJ, Sipski ML and Schleifer SJ. Alteration of immune system function in tetraplegics. A pilot study. Am.J.Phys.Med.Rehabil. 73: 387-393, 1994.
12. Cardenas DD, Hoffman JM, Kirshblum S and McKinley W. Etiology and incidence of rehospitalization after traumatic spinal cord injury: a multicenter analysis. Arch.Phys.Med.Rehabil. 85: 1757-1763, 2004.
13. Carpenter GH, Garrett JR, Hartley RH and Proctor GB. The influence of nerves on the secretion of immunoglobulin A into submandibular saliva in rats. J.Physiol. 512 ( Pt 2): 567-573, 1998.
14. Carpenter GH, Proctor GB, Anderson LC, Zhang XS and Garrett JR. Immunoglobulin A secretion into saliva during dual sympathetic and parasympathetic nerve stimulation of rat submandibular glands. Exp.Physiol. 85: 281-286, 2000.
15. Castellani JW, Armstrong LE, Kenefick RW, Pasqualicchio AA, Riebe D, Gabaree CL and Maresh CM. Cortisol and testosterone concentrations in wheelchair athletes during submaximal wheelchair ergometry. Eur.J.Appl.Physiol. 84: 42-47, 2001.
16. Cox AJ, Gleeson M, Pyne DB, Callister R, Hopkins WG and Fricker PA. Clinical and laboratory evaluation of upper respiratory symptoms in elite athletes. Clin.J.Sport Med. 18: 438-445, 2008.
17. Cruse JM, Lewis RE, Dilioglou S, Roe DL, Wallace WF and Chen RS. Review of immune function, healing of pressure ulcers, and nutritional status in patients with spinal cord injury. J.Spinal Cord Med. 23: 129-135, 2000.
18. Davies AL, Hayes KC and Dekaban GA. Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. Arch.Phys.Med.Rehabil. 88: 1384-1393, 2007.
19. Derrickson J, Ciesla N, Simpson N and Imle PC. A comparison of two breathing exercise programs for patients with quadriplegia. Phys.Ther. 72: 763-769, 1992.
20. Downing JE and Miyan JA. Neural immunoregulation: emerging roles for nerves in immune homeostasis and disease. Immunol.Today 21: 281-289, 2000.
21. Elenkov IJ, Wilder RL, Chrousos GP and Vizi ES. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. Pharmacol.Rev. 52: 595-638, 2000.
22. Frankel HL, Coll JR, Charlifue SW, Whiteneck GG, Gardner BP, Jamous MA, Krishnan KR, Nuseibeh I, Savic G and Sett P. Long-term survival in spinal cord injury: a fifty year investigation. Spinal Cord 36: 266-274, 1998.
23. Frey G, McCubbin J, Dunn J and Mazzeo R. Plasma catecholamine and lactate relationship during graded exercise in men with spinal cord injury. Med.Sci.Sports Exerc. 29: 451-456, 1997.
24. Frost RA, Nystrom GJ and Lang CH. Epinephrine stimulates IL-6 expression in skeletal muscle and C2C12 myoblasts: role of c-Jun NH2-terminal kinase and histone deacetylase activity. Am.J.Physiol.Endocrinol.Metab. 286: E809-17, 2004.
25. Furusawa K, Tajima F, Okawa H, Takahashi M and Ogata H. The incidence of post-race symptoms of upper respiratory tract infection in wheelchair marathon racers. Spinal Cord 45: 513-517, 2007.

26. Furusawa K, Tajima F, Tanaka Y, Ide M and Ogata H. Short-term attenuation of natural killer cell cytotoxic activity in wheelchair marathoners with paraplegia. Arch.Phys.Med.Rehabil. 79: 1116-1121, 1998.
27. Furusawa K, Tajima F, Umezu Y, Ueta M, Ide M, Mizushima T and Ogata H. Activation of natural killer cell function in recreational athletes with paraplegia during a wheelchair half-marathon race. Arch.Phys.Med.Rehabil. 84: 706-711, 2003.
28. Garshick E, Stolzmann KL, Gagnon DR, Morse LR and Brown R. Systemic inflammation and reduced pulmonary function in chronic spinal cord injury. PM R. 3: 433-439, 2011.
29. Garstang SV and Miller-Smith SA. Autonomic nervous system dysfunction after spinal cord injury. Phys.Med.Rehabil.Clin.N.Am. 18: 275-96, vi-vii, 2007.
30. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS and Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat.Rev.Immunol. 11: 607-615, 2011.
31. Gold JR and Gold MM. Access for all: the rise of the Paralympic Games. J.R.Soc.Promot.Health. 127: 133-141, 2007.
32. Goosey-Tolfrey V. Physiological profiles of elite wheelchair basketball players in preparation for the 2000 Paralympic Games. Adapt.Phys.Activ Q. 22: 57-66, 2005.
33. Goosey-Tolfrey VL, Foden E, Perret C and Degens H. Effects of inspiratory muscle training on respiratory function and repetitive sprint performance in wheelchair basketball players. Br.J.Sports Med. 44: 665-668, 2010.
34. Guerrero AR, Uchida K, Nakajima H, Watanabe S, Nakamura M, Johnson WE and Baba H. Blockade of interleukin-6 signaling inhibits the classic pathway and promotes an alternative pathway of macrophage activation after spinal cord injury in mice. J.Neuroinflammation 9: 40, 2012.
35. Held KS, Steward O, Blanc C and Lane TE. Impaired immune responses following spinal cord injury lead to reduced ability to control viral infection. Exp.Neurol. 226: 242-253, 2010.
36. Hettinga FJ, Valent L, Groen W, van Drongelen S, de Groot S and van der Woude LH. Hand-cycling: an active form of wheeled mobility, recreation, and sports. Phys.Med.Rehabil.Clin.N.Am. 21: 127-140, 2010.
37. Huang TS, Wang YH, Lee SH and Lai JS. Impaired hypothalamus-pituitary-adrenal axis in men with spinal cord injuries. Am.J.Phys.Med.Rehabil. 77: 108-112, 1998.
38. Hullemann KD, List M, Matthes D, Wiese G and Zika D. Spiroergometric and telemetric investigations during the XXI International Stoke Mandeville Games 1972 in Heidelberg. Paraplegia 13: 109-123, 1975.
39. Ibarra A, Jimenez A, Cortes C and Correa D. Influence of the intensity, level and phase of spinal cord injury on the proliferation of T cells and T-cell-dependent antibody reactions in rats. Spinal Cord 45: 380-386, 2007.
40. Iversen PO, Hjeltnes N, Holm B, Flatebo T, Strom-Gundersen I, Ronning W, Stanghelle J and Benestad HB. Depressed immunity and impaired proliferation of hematopoietic progenitor cells in patients with complete spinal cord injury. Blood 96: 2081-2083, 2000.
41. Jonsdottir IH. Special feature for the Olympics: effects of exercise on the immune system: neuropeptides and their interaction with exercise and immune function. Immunol.Cell Biol. 78: 562-570, 2000.
42. Kappel M, Tvede N, Galbo H, Haahr PM, Kjaer M, Linstow M, Klarlund K and Pedersen BK. Evidence that the effect of physical exercise on NK cell activity is mediated by epinephrine. J.Appl.Physiol. 70: 2530-2534, 1991.

43. Kawashima N, Nakazawa K, Ishii N, Akai M and Yano H. Potential impact of orthotic gait exercise on natural killer cell activities in thoracic level of spinal cord-injured patients. Spinal Cord 42: 420-424, 2004.
44. Keller SE, Weiss JM, Schleifer SJ, Miller NE and Stein M. Stress-induced suppression of immunity in adrenalectomized rats. Science 221: 1301-1304, 1983.
45. Kjaer M, Secher NH, Bangsbo J, Perko G, Horn A, Mohr T and Galbo H. Hormonal and metabolic responses to electrically induced cycling during epidural anesthesia in humans. J.Appl.Physiol. 80: 2156-2162, 1996.
46. Kliesch WF, Cruse JM, Lewis RE, Bishop GR, Brackin B and Lampton JA. Restoration of depressed immune function in spinal cord injury patients receiving rehabilitation therapy. Paraplegia 34: 82-90, 1996.
47. Klokker M, Mohr T, Kjaer M, Galbo H and Pedersen BK. The natural killer cell response to exercise in spinal cord injured individuals. Eur.J.Appl.Physiol.Occup.Physiol. 79: 106-109, 1998.
48. Kouda K, Furusawa K, Sugiyama H, Sumiya T, Ito T, Tajima F and Shimizu K. Does 20-min arm crank ergometer exercise increase plasma interleukin-6 in individuals with cervical spinal cord injury? Eur.J.Appl.Physiol. 112: 597-604, 2011.
49. Krassioukov A. Autonomic function following cervical spinal cord injury. Respir.Physiol.Neurobiol. 169: 157-164, 2009.
50. Landmann RM, Muller FB, Perini C, Wesp M, Erne P and Buhler FR. Changes of immunoregulatory cells induced by psychological and physical stress: relationship to plasma catecholamines. Clin.Exp.Immunol. 58: 127-135, 1984.
51. Leicht CA, Bishop NC and Goosey-Tolfrey VL. Mucosal immune responses during court training in elite tetraplegic athletes. Spinal Cord 50: 760-765, 2012.
52. Leicht CA, Bishop NC and Goosey-Tolfrey VL. Mucosal immune responses to treadmill exercise in elite wheelchair athletes. Med.Sci.Sports Exerc. 43: 1414-1421, 2011.
53. Leicht CA, Bishop NC, Paulson TAW, Griggs KE and Goosey-Tolfrey VL. Salivary immunoglobulin A and upper respiratory symptoms during five months of training in elite tetraplegic athletes. Int.J.Sports Physiol.Perform. 2011.
54. Lucin KM, Sanders VM, Jones TB, Malarkey WB and Popovich PG. Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. Exp.Neurol. 207: 75-84, 2007.
55. Lucin KM, Sanders VM and Popovich PG. Stress hormones collaborate to induce lymphocyte apoptosis after high level spinal cord injury. J.Neurochem. 110: 1409-1421, 2009.
56. McHale NG and Thornbury KD. Sympathetic stimulation causes increased output of lymphocytes from the popliteal node in anaesthetized sheep. Exp.Physiol. 75: 847-850, 1990.
57. Moynihan J, Kruszewska B, Madden K and Callahan T. Sympathetic nervous system regulation of immunity. J.Neuroimmunol. 147: 87-90, 2004.
58. Nagao F, Suzui M, Takeda K, Yagita H and Okumura K. Mobilization of NK cells by exercise: downmodulation of adhesion molecules on NK cells by catecholamines. Am.J.Physiol.Regul.Integr.Comp.Physiol. 279: R1251-6, 2000.
59. Nash MS. Immune dysfunction and illness susceptibility after spinal cord injury: an overview of probable causes, likely consequences, and potential treatments. J.Spinal Cord Med. 23: 109-110, 2000.

60. Nash MS. Known and plausible modulators of depressed immune functions following spinal cord injuries. J.Spinal Cord Med. 23: 111-120, 2000.
61. Nash MS. Immune responses to nervous system decentralization and exercise in quadriplegia. Med.Sci.Sports Exerc. 26: 164-171, 1994.
62. Nielsen S and Pedersen BK. Skeletal muscle as an immunogenic organ. Curr.Opin.Pharmacol. 8: 346-351, 2008.
63. Olive JL, Dudley GA and McCully KK. Vascular remodeling after spinal cord injury. Med.Sci.Sports Exerc. 35: 901-907, 2003.
64. Paulson TAW, Goosey-Tolfrey VL, Lenton JP, Leicht CA and Bishop NC. Spinal cord injury level and the circulating cytokine response to strenuous exercise. Medicine and Science in Sports and Exercise 2013 DOI: 10.1249/MSS.0b013e31828f9bbb
65. Pavlov VA and Tracey KJ. Neural regulators of innate immune responses and inflammation. Cell Mol.Life Sci. 61: 2322-2331, 2004.
66. Paynter DE, Tipton CM and Tcheng TK. Response of immunosympathectomized rats to training. J.Appl.Physiol. 42: 935-940, 1977.
67. Pedersen BK. Muscles and their myokines. J.Exp.Biol. 214: 337-346, 2011.
68. Pedersen BK and Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol.Rev. 88: 1379-1406, 2008.
69. Proctor GB and Carpenter GH. Regulation of salivary gland function by autonomic nerves. Auton.Neurosci. 133: 3-18, 2007.
70. Proctor GB, Carpenter GH and Garrett JR. Sympathetic decentralization abolishes increased secretion of immunoglobulin A evoked by parasympathetic stimulation of rat submandibular glands. J.Neuroimmunol. 109: 147-154, 2000.
71. Proctor GB, Garrett JR, Carpenter GH and Ebersole LE. Salivary secretion of immunoglobulin A by submandibular glands in response to autonomimetic infusions in anaesthetised rats. J.Neuroimmunol. 136: 17-24, 2003.
72. Pyne DB, Gleeson M, McDonald WA, Clancy RL, Perry C,Jr and Fricker PA. Training strategies to maintain immunocompetence in athletes. Int.J.Sports Med. 21 Suppl 1: S51-60, 2000.
73. Schmid A, Huonker M, Barturen JM, Stahl F, Schmidt-Trucksass A, Konig D, Grathwohl D, Lehmann M and Keul J. Catecholamines, heart rate, and oxygen uptake during exercise in persons with spinal cord injury. J.Appl.Physiol. 85: 635-641, 1998.
74. Schmid A, Huonker M, Stahl F, Barturen JM, Konig D, Heim M, Lehmann M and Keul J. Free plasma catecholamines in spinal cord injured persons with different injury levels at rest and during exercise. J.Auton.Nerv.Syst. 68: 96-100, 1998.
75. Smith BM, Evans CT, Kurichi JE, Weaver FM, Patel N and Burns SP. Acute respiratory tract infection visits of veterans with spinal cord injuries and disorders: rates, trends, and risk factors. J.Spinal Cord Med. 30: 355-361, 2007.
76. Soden RJ, Walsh J, Middleton JW, Craven ML, Rutkowski SB and Yeo JD. Causes of death after spinal cord injury. Spinal Cord 38: 604-610, 2000.
77. Spence L, Brown WJ, Pyne DB, Nissen MD, Sloots TP, McCormack JG, Locke AS and Fricker PA. Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. Med.Sci.Sports Exerc. 39: 577-586, 2007.
78. Starkie RL, Rolland J and Febbraio MA. Effect of adrenergic blockade on lymphocyte cytokine production at rest and during exercise. Am.J.Physiol.Cell.Physiol. 281: C1233-40, 2001.
79. Steensberg A, Fischer CP, Keller C, Moller K and Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am.J.Physiol.Endocrinol.Metab. 285: E433-7, 2003.

80. Steensberg A, Toft AD, Schjerling P, Halkjaer-Kristensen J and Pedersen BK. Plasma interleukin-6 during strenuous exercise: role of epinephrine. Am.J.Physiol.Cell.Physiol. 281: C1001-4, 2001.
81. Steinberg LL, Lauro FA, Sposito MM, Tufik S, Mello MT, Naffah-Mazzacoratti MG, Cavalheiro EA and Silva AC. Catecholamine response to exercise in individuals with different levels of paraplegia. Braz.J.Med.Biol.Res. 33: 913-918, 2000.
82. Stolzmann KL, Gagnon DR, Brown R, Tun CG and Garshick E. Risk factors for chest illness in chronic spinal cord injury: a prospective study. Am.J.Phys.Med.Rehabil. 89: 576-583, 2010.
83. Tonnesen E, Christensen NJ and Brinklov MM. Natural killer cell activity during cortisol and adrenaline infusion in healthy volunteers. Eur.J.Clin.Invest. 17: 497-503, 1987.
84. Ueta M, Furusawa K, Takahashi M, Akatsu Y, Nakamura T and Tajima F. Attenuation of natural killer cell activity during 2-h exercise in individuals with spinal cord injuries. Spinal Cord 46: 26-32, 2008.
85. Van Houtte S, Vanlandewijck Y and Gosselink R. Respiratory muscle training in persons with spinal cord injury: a systematic review. Respir.Med. 100: 1886-1895, 2006.
86. Vissing J, Wilson LB, Mitchell JH and Victor RG. Static muscle contraction reflexly increases adrenal sympathetic nerve activity in rats. Am.J.Physiol. 261: R1307-12, 1991.
87. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A and Simon P. Position statement. Part one: Immune function and exercise. Exerc.Immunol.Rev. 17: 6-63, 2011.
88. Wheeler G, Cumming D, Burnham R, Maclean I, Sloley BD, Bhambhani Y and Steadward RD. Testosterone, cortisol and catecholamine responses to exercise stress and autonomic dysreflexia in elite quadriplegic athletes. Paraplegia 32: 292-299, 1994.
89. Yamanaka M, Furusawa K, Sugiyama H, Goto M, Kinoshita T, Kanno N, Takaoka K and Tajima F. Impaired immune response to voluntary arm-crank ergometer exercise in patients with cervical spinal cord injury. Spinal Cord 48: 734-739, 2010.
90. Zeitzer JM, Ayas NT, Shea SA, Brown R and Czeisler CA. Absence of detectable melatonin and preservation of cortisol and thyrotropin rhythms in tetraplegia. J.Clin.Endocrinol.Metab. 85: 2189-2196, 2000.