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Review

Environmental factors, immune changes and respiratory diseases in troops during military activities☆

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ABSTRACT

Combat operations in contemporary theaters of war, as well as combat training, are carried out in all parts of the world, typically in a harsh environment. Specific environmental conditions, such as heat, cold, high-altitudes, desert climates, as well as chemical and biological pollution of both the atmosphere and soil, together with over-exertion, food restrictions, sleep deprivation, and psychological stress can all result in changes in the immune system and the occurrence of associated diseases. Respiratory diseases are one of the most common health problems among military personnel participating in combat training or deployed to operations in areas characterized by difficult climatic and sanitary conditions. They are, therefore, one of the main reasons for military personnel requiring ambulant and hospital treatment. The aim of the study was to discuss the influence of environmental factors and the conditions in which active duty is performed on changes in the immune system and the occurrence of respiratory tract diseases in a military environment.

1. Introduction

Military personnel deployed to operations in the contemporary battlefield and participating in combat training are at risk of contracting respiratory symptoms, as well as acute and chronic diseases. Specific inhalation exposures which are of concern to researchers include ambient desert dust, emissions from burn pits where waste products are incinerated, industrial pollutants, and airborne contaminants associated with degraded soil (Helmer et al., 2007). Other major health hazards are created by overexertion, stress, extreme air temperatures, and high altitude (Castell et al., 2010; Shephard et al., 2001). Epidemiological studies have demonstrated that deployed soldiers have higher rates of newly-reported respiratory symptoms than non-deployers (Smith et al., 2009). Recent studies suggest that obstructive airways diseases, including asthma and constrictive bronchiolitis, occur in troops returning from Iraq and Afghanistan (King et al., 2011; Szema et al., 2010). Acute respiratory diseases are the principle reason for out-patient treatment and hospitalization among military personnel, with an incidence exceeding that of the adult civilian population by up to three-fold. Adenoviruses, influenza A and B viruses, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, coronaviruses and rhinoviruses have been identified as the main causes of acute respiratory infections among the military population (Wang et al., 2010; Gray et al., 1999). Although these infective agents have been extensively studied, a significant proportion of illnesses (over 40%) has been caused by unknown causative agents (O'Shea et al., 2007). Limited diagnostic capabilities inside the area of operations make it difficult to accurately estimate the exact number of respiratory diseases (VonFeldt et al., 2012; Helmer et al., 2007). The aim of the study was to present the influence of environmental factors and the conditions in which active duty is performed on changes in the immune system as well as the occurrence of respiratory tract diseases in a military environment.

2. Environmental factors and respiratory diseases in soldiers deployed to military operations

Military personnel are often relocated to areas characterized by adverse environmental conditions (extreme heat and humidity, cold, high altitude or air pollutants) where they are required to perform strenuous physical activity (Castell et al., 2010; Helmer

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et al., 2007; Shephard et al., 2001). Leading exertion immunologists have suggested that physical activity performed in stressful environments poses a greater than normal threat to immune functions (Shephard and Shek, 1999). Over-exertion in hot conditions in which the core temperature rises by >1 °C compared with thermoneutral conditions, where the core temperature rise is <1 °C, augments the anticipated increases in the circulating stress hormones, including catecholamines and cytokines, with associated elevations in circulating leukocyte counts (Rhind et al., 2004). In recent years, some articles have implied there is a direct relationship between environmental exposures, such as burn pit smoke or possible geological particulate matter (PM) during deployments of U.S. soldiers to Iraq and Afghanistan and the development of serious and debilitating chronic pulmonary disease (Morris et al., 2011). Adverse health effects, including respiratory diseases, are the known consequences of exposure to high levels of PM with an aerodynamic diameter of less than 10 μm (PM_{10}) and, in particular, less than 2.5 μm ($PM_{2.5}$). The severity of the effect depends on the amount and duration of exposure, the physical and chemical characteristics of the PM, and health of the exposed individuals (Davidson et al., 2005). Exposure to crustal dust and sand storms, sometimes lasting for days, is particularly troublesome to deployed soldiers. This problem is exacerbated by severe degradation of the soil in some areas of Southwest Asia due to overuse by heavy vehicles, along with often poor environmental controls over local industries. Air sampling has shown high levels of $PM_{2.5}$ (the particulate size that is respirable and able to penetrate the small airways) in many places where soldiers participating in the Iraqi and Enduring Freedom operations are stationed. This dust may contain high levels of metals, including lead, and may impair the respiratory defense mechanism (VonFeldt et al., 2012; Engelbrecht et al., 2009). Exposure to smoke from burning oil wells caused concern during Operations Desert Shield/Desert Storm in 1990–1. Although oil well fires have not been of such concern in recent theaters of operations in Iraq and Afghanistan, exposure to smoke from other types of industrial fires has been regarded a health hazard. Reporting on the health effects of the Kuwait oil fires of 1991 among U.S. troops, survey research undertaken by Army investigators found an increase in the number of reported symptoms of upper respiratory tract irritation, shortness of breath, and coughing associated with proximity to the Kuwaiti oil fires. Sanders et al. (2005) conducted a survey of 15,000 redeploying military personnel from Iraq and Afghanistan and estimated that 69% had reported experiencing respiratory illnesses, of which 17% required medical care. A further survey, conducted by the Naval Health Research Center personnel on respiratory symptoms, found that deployed personnel had a higher rate of newly-reported respiratory diseases than non-deployed soldiers (14% vs. 10%). The authors suggested that specific exposures rather than deployment may be a determinant of post-deployment respiratory disease (Smith et al., 2009). A confounding factor in evaluating respiratory symptoms in deployed soldiers is the higher rate of tobacco use among military personnel and its increased use during deployment. A survey of soldiers deployed to Iraq reported that 51.9% of males and 41.7% of females were using tobacco before deployment, and 58.3% of males and 52.1% of females during deployment (DiNicola and Seltzer, 2009). Very limited data exists on the effects of military deployment on asthma (with an established diagnosis of asthma after the age of 12 being an exclusion criterion for deployment). Despite these restrictions, asthma remains a significant problem among military personnel on active duty. Nish and Schwietz (1992) evaluated 192 Air Force recruits for symptoms of exertional dyspnea and found that 45% of the examined patients had previously been diagnosed with asthma. Morris et al. (2002) found that nearly half of their active duty patients with exertional dyspnea had either asthma or exercise-induced bronchospasm. The extreme climatic conditions of Southwest Asia along with high PM exposures due to dust and sand storms could potentially contribute to poor asthma control with increased exacerbations. Roop et al. (2007) surveyed deploying Army personnel and found that 5% of troops deployed to Southwest Asia reported a previous diagnosis of this disease. A retrospective review of over 6000 veterans found higher rates of new-onset asthma in deployed U.S. military personnel in the years 2004–2007 compared with non-deployed military personnel stationed in the United States (6.6% vs. 4.3%) (Szema et al., 2010). Another health problem occurring among soldiers deployed to military operations over the last decade is constrictive bronchiolitis, a lung disease characterized by fixed airways obstruction and fibrosis of the distal airways or bronchioles. It is associated with occupational and environmental inhalation exposures, e.g. nitrogen and sulfur dioxides, inorganic dust, and may cause permanent respiratory impairment. King et al. (2011) presented data concerning 80 U.S. soldiers, with inhalational exposures during service in Iraq and Afghanistan, and with symptoms of what was primarily exertional dyspnea while running. Most patients had normal spirometry and high-resolution computed tomography scans of the chest. The results of physical examinations of the chest were normal in all the patients. Thirty eight of these soldiers underwent a lung biopsy which revealed pathologic changes consistent with constrictive bronchiolitis. Twenty eight of the individuals reported exposure to smoke from a fire in a large sulfur mine near Mosul (Iraq). The other soldiers reported exposure to dust storms, increased solid waste in burn pits, incinerated human waste. The next unusual disease is acute eosinophilic pneumonia, characterized by acute respiratory failure, bilateral pulmonary infiltrates, hypoxia, and predominant eosinophila on bronchoalveolar lavage, which occurred among eighteen U.S. soldiers deployed to Kuwait and Iraq in the years 2003–2004. There were two deaths reported from this cohort. Most individuals reported exposure to fine airborne dust, and all used tobacco, with 78% reporting that they had recently started smoking. New-onset smoking was considered a risk factor in these patients (Shorr et al., 2004). Abraham et al. (2012) focused on obstructive pulmonary disease encounters, as these conditions are potentially related to in-theater environmental exposures (they constituted 7–10% of all respiratory system diagnoses among over 51,000 examined soldiers during pre- and postdeployment periods). Researchers observed statistically significant increases in the encounter rates for obstructive respiratory diseases from the pre- to post-deployment periods for single deployers.

Environmental exposures such as inhalation of dust, smoke, fumes, and aerosols are common in the deployment environment in Iraq and Afghanistan, and are suspected to adversely affect respiratory health among soldiers (Engelbrecht et al., 2009). Particulate matter in the Southwest Asia region is a primary exposure concern among the US military due to clouds of sand and dust, emissions from petrochemical and other industrial sites, burn pits used for waste disposal, and oil fields and fires (Abraham et al., 2012). During a military operation, soldiers generate vast amounts of waste each day which should be burned in pits or trucked to landfills, which are often unavailable. The open burning of solid and chemical wastes has been the usual practice in areas of Iraq and Afghanistan where military personnel are stationed. Open air burn pits with limited pollution controls generate smoke with highly variable components. Increasing concern about burn pit combustion product exposures is being expressed by returning troops (Engelbrecht et al., 2009).

The location, duration, and frequency of deployment are factors that may entail the risk of respiratory symptoms and should be documented in soldiers' medical history. Unexplained chest symptoms, abnormal spirometry, or a documented and substantial decline in physical fitness testing ability should prompt further diagnostic evaluation and consideration for referral to a pulmonary specialist (Helmer et al., 2007). When post-deployment soldiers are referred to a pulmonologist for an evaluation of respiratory symptoms, the approach taken should include occupational, environmental, and medical histories along with complete pulmonary function tests (PFTs) and a high resolution computed tomographic (HRCT) scan of the chest. The pulmonary function tests should include lung volumes pre- and post-bronchodilators, spirometry, and a test of the diffusing capacity of the lungs for carbon monoxide. The HRCT should include both inspiratory and expiratory views and prone/supine imaging. Other tests should be considered in the case of patients with post-deployment lung symptoms, e.g. metabolic exercise testing to assess for ventilator, cardiac, and gas exchange abnormalities (VonFeldt et al., 2012; Helmer et al., 2007).

3. Changes in immunity and respiratory tract syndromes during combat training

Over the past two decades, there have been numerous investigations examining the association between changes in the immune parameters and the risk of respiratory tract syndromes (RTS) in heavy exercising and non-exercising populations (Bishop and Gleeson, 2009; Shephard, 2010). The production of secretory immunoglobulin A (sIgA) is the major effector function of the mucosal immune system providing the 'first line of defence' against pathogens. More recently, the importance of other antimicrobial proteins in saliva (e.g. α-amylase, lactoferrin and lysozyme) has gained greater recognition (Walsh et al., 2011). Moderate exertion has little impact on mucosal immunity, but prolonged exercise and intensified training can lead to decreases in saliva secretion of sIgA. The mechanisms underlying the alterations in mucosal immunity with acute overexertion are related to the activation of the sympathetic nervous system and its associated effects on salivary protein exocytosis and IgA transcytosis. The reduced secretion of sIgA into the saliva during periods of intensified training and chronic stress are probably linked to the altered activity of the hypothalamic–pituitary–adrenal axis, with inhibitory effects on IgA synthesis and/or transcytosis. Consensus exists that reduced levels of saliva sIgA are associated with an increased risk of respiratory tract infections (RTI) during heavy training (Walsh et al., 2011). Also, cytokine plays an important role in modulating post-exertion changes in immune function that increase the risk of infection or the occurrence of inflammatory symptoms (Suzuki et al., 2002). The pro-inflammatory responses to exertion have the potential to be involved in expression of RTS that mimic RTI. A recent study of cytokine gene polymorphism by Cox et al. (2010) identified an underlying genetic predisposition to high expression of the pro-inflammatory interleukin-6 (IL-6) in people under over-exertion who are prone to frequent RTS. These studies add further weight to the evidence that suggests infections are not the only cause of 'sore throat' symptoms.

In response to acute exertion, a rapid interchange of immune cells between peripheral lymphoid tissues and the circulation occurs. The response depends on many factors, including the intensity, duration, and mode of exercise, concentrations of hormones and cytokines, changes in body temperature, blood flow, hydration status, and body position. Of all immune cells, natural killer (NK) cells, neutrophils, and macrophages appear to be the most responsive to the effects of acute exertion, both in terms of number and function. Exertion is also important in the context of stress influencing immune and hormonal functions. Strenuous training induces a physiological stress response and increases circulating concentrations of norepinephrine, epinephrine, cortisol, and other stress-related factors including cytokines (Hackney, 2006). Effective immunoprotection requires the rapid redistribution and recruitment of leucocytes into sites of potential infection. Some studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood (Dhabhar et al., 1996).

Likewise, there is a close interaction between immune function and sleep. Associations have been observed between abnormalities in the immune system and various forms of sleep disruption, which are of interest to exertion experts. The issues include sleep deprivation, shift work/duty, and disturbances of the circadian rhythm associated with latitudinal travel. One such study found that keeping healthy volunteers awake between 10 p.m. and 3 a.m. led to decreases in both total natural killer (NK) cell activity and activity per NK cell, together with a decrease in concanavalin-stimulated interlukin-2 (IL-2) production. After a night of recovery sleep, NK cell activity was restored, but IL-2 remained depressed (Irwin et al., 1996). More prolonged sleep deprivation leads to increases in leukocyte, granulocyte and monocyte counts and the proportion of lymphocytes in the S phase of the cell cycle, with enhanced NK cell activity, interferon production, IL-1 and IL-2 activity, and increased levels of C-reactive protein (Dinges et al., 1994).

Diagnosis of infections as the cause of RTS has recently come under scrutiny (Cox et al., 2008). There are people identified who, under over-exertion, suffer recurrent episodes of upper respiratory tract diseases, but who require a more exhaustive medical assessment in order to exclude non-infectious causes of the respiratory symptoms, such as allergy, autoimmune disorders, vocal cord dysfunction and unresolved non-respiratory infections. These studies identified that approximately one-third of RTS are caused by infection (bacterial, viral pathogens), one-third are due to a non-infectious cause, while the remaining third are of unknown etiology. The speculative causes of the 'unknown-etiology' group could include physical and mechanical damage such as drying of the airways (Bermon, 2007), asthma and allergic airway inflammation (Helenius et al., 2005), or psychological impacts of exertion on immunity (Bjermer and Anderson, 2005). Multiple physical and psychological stressors are likely to induce neurological and endocrine responses in addition to alterations in the immune parameters; these share common exertion-induced pathways that could result in RTS.

Numerous observations concerning immune changes and the incidence of RTS during over-exertion in soldiers are noticed in combat training carried out in a harsh environment. One of the most physically and psychologically demanding military training courses in the world is the U.S. Army Ranger Training Course. It lasts for 62 days and involves food restriction, sleep deprivation, and geographical challenges (forest, mountain, swamp, and desert exposures). Recruits participating in this course have demonstrated, in laboratory examination, a leukocytosis, a decrease in the number and percentage of T cells (helper, suppressor, and pan T cells), a suppression of lymphocyte proliferation, a decrease in the release of the soluble IL-2 receptor to phytohemagglutinin, and in the medical examination, an increase in the incidence of upper respiratory tract infections (Moore, 1992; Kramer et al., 1997; Shephard et al., 2001). Another example of immune changes during combat training is a 5-day military course following 3 weeks among a group of French Army soldiers. The combination of continuous heavy physical activity and sleep deprivation led to energy deficiency. At the beginning of the training program and immediately after the combat course, saliva samples were assayed for sIgA and plasma samples were assayed for IL-6, and also dehydroepiandrosterone sulfate, prolactin, catecholamines, and glucocorticoids. Secretory IgA was lower and circulating IL-6 was increased by the end of the course, which was attributed to sympathoadrenergic stimulation. Prolonged and repeated exercise such as that encountered in a military training program induced immune impairment via a decrease in mucosal immunity and a release of IL-6 into the circulation. The observed immune changes correlated to clinical findings on respiratory tract illnesses (Gomez-Merino et al., 2003). The immunosuppressive and inflammatory effects of the training may have stemmed from hormonal actions. For instance, training induced norepinephrine release as a consequence of the stimulation of sympathetic nerve terminals. Military training reduces the levels of two immunomodulatory hormones, DHEA (dehydroepiandrosterone) and prolactin, which is attributed to its stressful nature (Gomez-Merino et al., 2003). The body is often exposed to combinations of stressors, especially in military training where stressors are often prolonged, hard, continuous physical exercise combined with sleep, energy, and water deficiency, time pressure, or periods of waiting and inactivity (Gomez-Merino et al., 2003). In a study of the effects of food restriction during military training on T lymphocyte, Kramer et al. (1997) found proliferative responses in vitro (a reduction in the T lymphocyte response was noticed if the soldiers had a restricted diet). Booth et al. (2003) investigated the health and psychological effects of combat ration pack (CRP) feeding during 12 days of military training in a tropical environment. Among soldiers fed with CRPs mild symptoms of weight loss, suppressed immune function (both cell-mediated and humoral), loss of visceral protein, increased fatigue and feelings of confusion were observed.

Both physical activity and exposure to environmental stressors such as cold, heat, and high altitudes modify various components of the immune function: T cell counts, natural killer (NK) cell counts, and cytolytic activity, cytokine secretion, lymphocyte proliferation and immunoglobulin levels. Light physical activity or a moderate level of environmental stress stimulate the immune response, but exhausting physical activity or more severe environmental stress have a suppressant effect, manifested by a temporary increase in susceptibility to respiratory infections. Cold, dry air causes bronchospasm. It also depresses the tracheal ciliary function and increases the viscosity of tracheal mucus. Furthermore, whole-body cooling may facilitate the proliferation of some microorganisms. All of these factors tend to increase a person's susceptibility to upper respiratory infections (Shephard, 1998). Factors that modify white cell counts during an episode of hypothermia include increases in cardiac output and plasma catecholamine levels, and the secretion of cortisol (which induces a migration of neutrophiles out of the bone marrow into the tissues). Parallels can be drawn between certain manifestations of severe heat stress and the multiple organ distress syndrome of severe sepsis (Kappel et al., 1991). In long-term trials, hypoxia during high-altitude exposure might increase reliance upon glycogen and amino acids as fuels for exercise, thus reducing the plasma concentrations of key nutrients required by lymphocytes. Tissue hypoxia could also enhance local inflammatory responses in the active muscles, increasing oxidative stress during exertion. Finally, the exacerbation of lack of local oxygen by exertion could facilitate the penetration of endotoxins through the ischemic gut wall (Simon-Schnass, 1994). T cell function is decreased by 35–50% for more than three hours after prolonged and intensive exercise. The decrement in T cell function is caused by inhibition by plasma cortisol and norepinephrine, and exercise-induced alterations in blood concentrations of lymphocyte subsets. Natural killer (NK) cells usually react rapidly to viruses and bacteria, initially controlling them until the antigen-specific immune system begins to respond. Thus, the cytoxic activity of NK cells (NKCA) represents a major first line defense system against infection. As a result of prolonged exertion, NKCA is decreased by 35–60% for several hours. The decrease is most likely to be caused by the transfer of NK cells from the circulation to other tissue compartments including the muscles. In addition to mitogen-induced lymphocyte proliferation and NKCA, neutrophil phagocytic function and sIgA concentration are also reported to have been suppressed for several hours during recovery from prolonged intensive endurance exercise. During this 'window of decreased host protection', viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection (Nieman, 1995).

Lange et al. (2003) examined the health status of over 21,000 U.S. soldiers taking part in military training conducted in the Mojave Desert. Researchers noticed that healthy, young adults exposed to high-levels of soil-derived dust may have increased susceptibility to respiratory infectious illnesses after prolonged exposures to desert environments. The increased risk was largely attributable to excess hospitalizations for pneumonia and influenza. Whitham et al. (2006) studied paratroopers for 19 weeks, training at sea level. Their main findings were an increase in RTI in weeks 2 and 3, and a progressive decrease in the salivary flow rate during the study, which might have led to hypohydration. Mäkinen et al. (2009) found that cold temperature and low humidity were associated with an increased occurrence of respiratory tract infections. There are several suggested pathophysiological mechanisms to explain how exposure to cold could increase the occurrence of RTI. Although surrounded by controversy, the available laboratory and clinical evidence suggests that either the inhalation of cold air, cooling of the body surface or cold stress causes pathophysiological responses that may contribute to an increased susceptibility to respiratory infections. Although controversial, cold stress could also alter the immune system and affect susceptibility to RTI. Castell et al. (2010) investigated the potential biochemical markers of stress and fatigue, and RTI symptoms as a surrogate of immunodepression, in a group of US Marines undergoing intensive winter training at a high altitude. Selected plasma amino acids and leptin were measured as possible markers of fatigue and immunodepression, together with non-esterified fatty acids and total antioxidant capacity. Changes were observed in plasma free tryptophan, glutamine, leptin, non-esterified fatty acids, and total antioxidant capacity but not branched-chain amino acids. There was a marked decrease in free tryptophan. Resting glutamine decreased overall after one month at a high altitude. Glutamine routinely decreases 1–2 h after prolonged exercise. The authors observed early morning decreases in glutamine, suggesting the cumulative effect of prolonged activity, stress, and fatigue. Individuals with the highest illness scores had the greatest glutamine decrease, which may be associated with a diminished tolerance to stress. The degree of stress associated with military operations is much increased. Physical and psychological demands can be exacerbated by sleep deprivation, inadequate caloric intake, and a disruption to normal sleep/rest/eating cycles. Changes in environmental conditions and the individual's adaptive response to exposure all contribute to the degree of stress-related impairment of the immune function and the consequent susceptibility to opportunistic infectious agents.

Military recruits experience a high incidence of respiratory diseases, including febrile upper respiratory infections, pneumonia, pharyngitis, and bronchitis, leading to significant morbidity and lost training time. Adenoviruses, influenza A and B viruses, and *Streptococcus pyogenes* are implicated in over half of the febrile respiratory illness (FRI) cases reported at recruit training center clinics, while the etiology of the remaining cases is unclear (Wang et al., 2010). Numerous studies and reports covering the last twenty years suggest a high incidence of respiratory tract diseases during combat training and military operations carried out in difficult environmental conditions. Factors contributing to an increase in RTI susceptibility include the combined effects on the immune function of work that is heavy in relation to the individual's physical condition, over-exertion, food restriction, and psychological stress. Participating in military training or deployment to military operations does not appear to cause a clinically significant decrease in the immune function. If a soldier is allowed to adapt progressively over a longer period of training or operation, resting immune function may be enhanced (Shephard et al., 2001).

4. Summary

Respiratory diseases are one of the most common causes of acute infections among soldiers. Military personnel is at a particularly high risk of developing respiratory tract syndromes because of stressful duty, a harsh environment, and exposure to novel pathogens in disease-endemic areas during deployments. In a population of military personnel on active duty and participants in contemporary combat operations, researchers have observed an increase in post-deployment respiratory tract diseases and medical encounters for obstructive pulmonary diseases, compared with pre-deployment rates. Combat training programs in a military environment are usually very rigorous, involving not only prolonged periods of strenuous physical activity but also exposure to psychological stressors, sleep deprivation, a negative energy balance, shifts in the circadian rhythm, and exposure to hot, cold, and high-altitude environments. The effects of such challenges on a soldier's health are complex, resulting in a broad spectrum of changes in the immune system and numerous cases of various diseases, with a predominance of respiratory tract infections.

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