Immunoendocrine interactions and T cell proliferation responses to layered physical and psychological stressors

By

Jacob A. Siedlik

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Chairperson Philip M. Gallagher

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Stephen H. Benedict

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Trent J. Herda

_____

John P. Vardiman

_____

Joseph P. Weir

Date Defended: March 29, 2016

The Dissertation Committee for Jacob A. Siedlik

certifies that this is the approved version of the following dissertation:

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Chairperson Philip M. Gallagher

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Abstract

Introduction: Military training environments are rigorous requiring service men and women to endure not only physical and psychological stress but also sleep deprivation, caloric restrictions, and severe thermic challenges. Exposure to these layered stressors are thought to improve human performance by acclimating the individuals to "real-world" operational stressors. It is difficult for scientists to identify pertinent immunoendocrine interactions occurring in layered stress environments because of considerable logistical constraints involving location of and access to affected personnel. The convention has been to use immunoendocrine responses induced by various exercise regimens as platforms to generalize results to the layered, and more exaggerated stress environments of military training. **Methods:** Three distinct experiments were conducted to understand immunoendocrine interactions resulting from layered stress environments. The first project investigated T cell proliferation following concurrent aerobic and resistance training as well as assessing changes in measures of proliferation following delayed cell isolation protocols. The second project examined whether the exercise models we use to generalize to military experiences are accurate. Eight healthy males underwent a high intensity training session combining physical and psychological stress similar to that experience in military operational training. A control group of 8 subjects participated in a moderate intensity session as comparison. Blood parameters were measured at Pre, Post, 1 hr, 4hr, and 6hr. The third project was an observational study examining immunoendocrine responses to the Marine Corps Martial Arts Training Program (MCMAP). Thirty-six newly enlisted, male Marines were observed three times over a nine-week period at Fort Leonard Wood, MO. Blood parameters were measured prior to training, Post training and at 15 min intervals out to 1 hr after training cessation. **Conclusions:** Immunoendocrine alterations following MCMAP sessions are in line with current laboratory findings that examine response to paired physical and psychological stressors

suggesting MCMAP may be a good real world analogue of laboratory based layered stress experiments. The higher intensity training sessions utilized in study two generated an enhanced proliferative response similar to that observed from exercise in competitive settings suggestive of a psychologically driven mechanism for proliferation.

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Table of Contents

Chapter 1: Introduction

1. **Background**

Acute bouts of moderate and high-intensity exercise induce transient shifts in peripheral blood biomarkers resulting from the combined physical and psychological demands of the given effort. Exercise-induced alterations of specific immune cell populations and hormonal concentrations are some of, if not the most, commonly reported effects in the field of exercise immunology. The most consistent of these effects is the rapid mobilization of leukocytes and lymphocytes into peripheral circulation during exercise (1-4). Disruptions in leukocyte trafficking are thought to result from multiple stimuli including shear forces and hydrostatic pressure from surges in cardiac output (5, 6), additional lymphatic fluid pushed out by forceful muscle contractions (5) and as a response to increased concentrations of catecholamines (7) and glucocorticoids (1) in the blood.

Exercise-associated increases (lymphocytosis) and decreases (lymphocytopenia) in peripheral immune cell concentrations have been reported on extensively (8-10). Information regarding alterations in cell trafficking, however, offers little information about the overall immunocompetence of an individual following exercise. Upon encountering cognate antigen, a lymphocyte undergoes clonal expansion to increase the number of lymphocytes present with identical antigen specificity and defend the host from the threat (11). This proliferative capacity is a crucial feature of the adaptive immune response and a failure to do so in response to foreign antigen is indicative of impaired immune function (12). Because lymphocytes play a pivotal role in the immune response, it is important that investigations of susceptibility to infection following exercise be conducted within the context of proliferative capacity.

Accumulated evidence indicates that singular encounters of a physically or psychologically stressful nature lead to increased concentrations of catecholamines and

glucocorticoids, both of which can suppress immune function. While interpreting data of this sort it is important to remember that in the everyday environment it is rare that an individual is exposed to only a physical or psychological challenge alone. Whether it is psychological stress as part of competition (i.e. competitive triathlon or marathon) or stress related to occupational hazards (i.e. firefighting or military operations), there are a variety of ways individuals experience simultaneous psychological and physical stress in practical scenarios. This combination of stressors will, for the purposes of this review, be referred to as a dual stress challenge. Recently, scientists have begun investigating the role of dual stress challenges on endocrine physiology and they are finding enhanced sympathetic activation and adrenal responses following dual stress challenges (13-16). The mechanism(s) for this type of exacerbated response are unknown but the response itself indicates there may be a synergistic interaction in the dual stress response. Quantification of the functional immune response to dual stress challenges can potentially improve our understanding and development of wellness interventions for high-stress occupations (i.e. firefighter, law enforcement, and military) that, by the very nature of the job, are repeatedly exposed to combined physical and psychological stress. Therefore, the aim of these studies is to provide a better understanding of changes in immunocompetence following exposure to dual stress challenges in humans.

1.2 Specific Aims

Immunoendocrine interactions derived from the physiological stress response have profound effects on performance, cognitive processes, and organismal health. Improved understanding of how immune function is altered in response to single and dual stress events of moderate and high

intensities will advance the field of exercise immunology, particularly in terms of the practical application of results.

This proposal consists of three separate projects. Study One investigates changes in immunocompetence following either an exercise or control condition. The emphasis will be placed on measuring T cell activation through cluster of differentiation (CD) 25, a surface marker specific to T cell activation. Study Two examines acute stress-induced changes in immune markers, including *in vitro* lymphocyte proliferation, following either a moderate intensity exercise trial or a vigorous layered stress challenge delivered in a military style environment. Study Three examines perturbations in immunoendocrine markers following Marine Corps Martial Arts training.

1.2.1 Study 1: T cell Activation Following an Acute Bout of Concurrent Aerobic and Resistance Exercise

T cell proliferation is a sequential process and few exercise-driven studies have investigated discrete elements of this sequence (17, 18). CD25, also known as the interleukin 2 receptor (IL-2R), is linked to immune activation by way of its interaction with IL-2, a potent T cell growth factor (19, 20). CD25 has relatively low expression in resting T cells but is quickly upregulated in response to IL-2 mediated signaling (21, 22). IL-2 signaling is crucial for T cell expansion and, consequently, any change in CD25 expression potentially disrupts the proliferative response.

Specific Aim 1: Determine how CD25 expression in T cells is altered following 30 min of a combined moderate aerobic and anaerobic exercise protocol.

Hypotheses: We hypothesized that CD25 expression would be upregulated following an exercise protocol consisting of 15 min of aerobic exercise and 15 min of resistance exercise. Intensity of exercise was modified to maintain a rate of perceived exertion (RPE) of approximately 15. **Approach:** To test this hypothesis total T cells were isolated from peripheral blood by negative selection using a Human T cell enrichment kit. T cell proliferation was analyzed in response to either co-stimulation through CD3+CD28 using plate-bound antibodies, phytohaemagglutinin (PHA), or no simulation. Cells were incubated for 7 d at 37˚ C in a humidified incubator with 5% CO_2 and then analyzed by flow cytometry.

Specific Aim 2: Determine if changes in T cell proliferative ability and surface marker expression of CD25 following exercise are stable when blood processing is delayed 24 h.

Hypotheses: We hypothesized that CD25 expression and measures of proliferation following exercise would be decreased if T cell isolation from whole blood is delayed by 24 h. **Approach:** Two extra vials of blood were collected at both the baseline and post-training time points in addition to the vials used to address Aim# 1. One vial rested overnight at room temperature prior to T cell isolation and the other rested overnight at 4˚C. T cell isolation procedures were the same as those utilized for Aim 1.

1.2.2 Study 2: Do Military and Tactical Experiences Model the Characteristic Exercise Response

Military physical training programs are generally rigorous in nature and involve periods of intense physical activity, psychological stress, sleep deprivation, and exposure to extreme environments (23). The combined effects of these layered stressors on a trainee's immune system

are complex in nature and may be deleterious as evidenced by wartime immunosuppression in active-duty military personnel (24). Recently, it has been reported that the combination of physical and psychological stressors leads to enhanced sympathetic activation and adrenal responses following combined stress challenges (13-16).

A study investigating immunoendocrine responses to combined physical and psychological stressors in professional firefighters found a greater increase of norepinephrine (NE), epinephrine (EPI), and IL-2 in a dual challenge condition when compared to exercise alone (13). The authors did not, however, utilize a functional measurement of immunocompetence. This study will clarify whether a tactical experience is similar in scale and nature to current exercise and dual challenge stress designs.

Specific Aim 1: Determine whether T cell proliferative capacity is differentially effected by exposure to a high intensity, dual stress environment relative to a moderate intensity, single stress challenge.

Hypothesis: We hypothesized that T cell proliferative capacity would be significantly suppressed in the high stress condition compared to the moderate intensity controls. **Approach:** T cell proliferation was analyzed in response to co-stimulation through CD3+CD28 using plate-bound antibodies, PHA treatment, or no simulation.

Specific Aim 2: Determine whether immunomodulatory cytokines and/or damage associated molecular patterns (DAMPs) are enhancing or suppressing the T cell functional response to the testing session.

Hypothesis: We hypothesized that oxidative stress following exercise would modulate T cell activity through immunomodulatory cytokines and DAMPs. **Approach:** Peripheral concentrations of the major cytokines IFN-γ, IL-10, IL-17a, IL-1β, IL-2, IL-4, IL-5, IL-6, and TNF-α, were determined using a human cytokine magnetic bead panel kit. High mobility group box 1 protein (HMGB1) was assessed by ELISA.

Specific Aim 3: Determine if high intensity stress causes greater perturbations in leukocyte concentrations in peripheral blood versus moderate intensity stress condition.

Hypothesis: We hypothesized that the leukocyte trafficking in the peripheral blood would be greater in the high intensity stress group and that these changes would be associated with endocrine measures. **Approach:** We measured these differences using commercially available ELISA kits.

1.2.3 Study 3: Immunoendocrine responses to the Marine Corps Martial Arts Program

The focus of the Marine Corps Martial Arts Program (MCMAP) is the personal development of each Marine in a team framework using a standardized, trainable, and sustainable close-combat fighting system that will both prepare and acclimate them to the rigors of training and deployments. The MCMAP is intentionally delivered in an environment characterized by periods of intense physical activity and psychological stress and is intended to develop the physical skills and character necessary for the Modern Marine. Our goal within the context of this training environment is to quantify immunoendocrine recovery profiles following MCMAP training for entry level, enlisted, male Marines.

Specific Aim 1: Quantify the immunoendocrine profiles over a one-hour recovery period following acute bouts of MCMAP training.

Hypothesis: We hypothesized that all immunoendocrine parameters would be significantly altered with respect to time post-training. **Approach:** Peripheral concentrations of both catecholamines and cortisol along with leukocyte and lymphocyte subsets were assessed as part of this protocol. These differences were measured using commercially available assays.

Specific Aim 2: Develop a battery of visualized trend lines equations and predictive regression equations for how individual immunoendocrine parameters interact within Marines in the MCMAP program.

Hypotheses: We hypothesized that fluctuations in immunoendocrine parameters would vary slightly over repeated exposures to training. **Approach:** Physiological biomarkers were measured through commercially available assays. Analyses of effects were performed using multilevel regression models.

Chapter 2: Immunoendocrine Interactions and T Cell Proliferation

2. Introduction

The immune system is a complex system of multiple cell-types that communicate to protect and repair the body. One of the many ways the immune system maintains organismal homeostasis is through direct and continuous communication with the endocrine and central nervous systems (CNS). Chronic dysregulation of the immune system can be problematic and lead to attenuated immune responses and increased rates of sickness. One of the major insults to the immune system is stress. Stressors, both physical and psychological, can impair the immune response via dysregulation of the endocrine system and CNS. The sympathetic-adrenal medullary (SAM) and the hypothalamic-pituitary-adrenal (HPA) axes are direct pathways by which immune disruptions occur in response to stressful conditions. A variety of immune cells express receptors for SAM and HPA hormones and their responses range from disruptions in cell trafficking to suppression of lymphocyte proliferative capacity. The proliferative response of lymphocytes to mitogens following exercise-specific stress has been extensively reported but the results have been inconsistent. Methodological issues related to mitogen selection and cell culture methods have hampered the ability to make adequate conclusions regarding the role of intense exercise in suppressing immune function. This review will address the role of acute exercise, a major physical stress, on the systemic interactions of the immune system, with a particular focus on understanding of the mechanisms underlying the functional immune response as measured through lymphocyte proliferative capacity.

2.2 The Immune System

Humans are constantly exposed to foreign pathogens that either lie on the skin or are exposed to the lumen by the normal physiological duties of the respiratory and digestive tracts.

Most pathogens fail to breach the organismal system due to immediate barriers like the skin, mucosal membranes, and membrane and peptide breakdown by the low pH environment of the stomach. These protective mechanisms are generally enough to prevent infection but pathogens that ultimately enter the system are often quickly eliminated by phagocytic cells or soluble factors like lysozymes or interferons. Beyond these simple barriers, the immune system is an adaptive and highly complex network of lymphoid organs, differing cell types, humoral factors, chemokines and cytokines that identify and target potentially harmful substances. The two major components of the immune response are the ability to target specific antigens (e.g. antibodies) and the ability to differentiate between self and non-self. The ability to discriminate between self and target invading pathogens allows for rapid removal of specific foreign objects while protecting the 'self' from unwarranted attack. Molecular recognition of this sort is a result of intricate interactions between cellular ligands and/or signaling proteins with surface receptors on the involved cells (11).

The immune system is composed of the innate immune system and the acquired immune system. The innate immune system is comprised of monocytes, granulocytes (neutrophils, basophils, eosinophils) and dendritic cells. These cells circulate in the blood to identify pathogen associated molecular patterns (PAMPs) on microbes using toll-like receptors (TLR) and other pattern recognition receptors [PRR; (11)]. PRRs allow cells to accurately identify structural patterns common to microbial agents for purposes of opsonization, complement activation, phagocytosis, and activation of inflammatory processes (25, 26). The innate immune system acts as a fast and aggressive response for detection and elimination of foreign pathogens and can be characterized as the inflammatory response. It is not, however, particularly specific or adaptive.

This inflammation response is generated from detection of shared structural motifs, not specific antigens, and there is no institutional memory to improve the response to repeated exposures.

Acquired immunity is the result of repeated exposure and institutional memory and, as a result, has a slower and more specific response. Acquired immunity takes advantage of antigen specificity, the diversity of recognition molecules, immunological memory of pathogens and the ability to differentiate between self and non-self (11). Unlike leukocytes of the innate immune system, the lymphocytes of acquired immunity are capable of identifying single amino acid differences in protein structures, allowing for tremendous diversity in antigenic specificity. Moreover, acquired immune cells are able to learn and retain information from the first exposure to a specific antigen, which heightens the immune response to subsequent exposures (11).

2.2.1 Lymphocytes

Primary lymphocytes originate from stem cells in the bone marrow and are classified as T cells or B cells. T cells mature in the thymus while B cells remain in the bone marrow until maturation (11). Together T and B cells are the primary effector cells of humoral and cell-mediated immunity. Humoral immunity is driven through the production and secretion of antibodies which, when bound to their specific antigen, facilitate immune responses such as phagocytosis. The cell-mediated immune response is a function of direct cell-to-cell contact with T cells binding and attacking specific virus-infected or otherwise dangerous (i.e. neoplastic) cells (11).

2.2.2 B Cells

B cells are antibody producing lymphoid cells and mediators of the humoral immune response typically identified by the clusters of differentiation (CD) 19 surface marker and account for ~5-15% of circulating lymphocytes (27). B cell activation occurs predominately through T cell dependent (TD) and T cell independent (TI) antigens (28). TD antigens are first bound by dendritic cells and processed through endocytic pathways to present peptides of the class II major histocompatibility complex (MHC) to antigen specific T cells. Once activated, T cells upregulate expression of CD40L which binds to a CD40 receptor on B cells to stimulate further B cell activation (27-30). Activated T cells can further stimulate B cells through secretion of interferon-γ (IFN- γ), interleukin (IL)-2, IL-4 and IL-6. IL-4 and IL-6 are of note as they can stimulate B cell activation and plasma cell differentiation, respectively (27).

TI antigens do not require degradation and presentation on class II MHC. TI antigens are further classified as type 1 (TI-1) and type 2 (TI-2). TI-1 are polyclonal activators of B cells that bind to TLR on the surface of cells (30). TI-2 antigens tend to be of large molecular weight with repeating antigenic epitopes that cross-link B cell receptors (BCR) directly (28). The BCR is a membrane-embedded antibody on the B cell surface that functions as the specific antigen binding site (11). TI-2 antigens do not require direct contact with T cells to generate B cell activation but appear to require T cell dependent cytokine secretions (27).

2.2.3 T Cells

T cells are identified by the CD3 surface marker and make up 60-85% of circulating lymphocytes (11). These lymphocytes are further differentiated based on expression of CD4 or CD8 surface markers, markers that define antigen recognition abilities through either class II (CD4) or class I MHC restrictions (CD8). $CD4^+$ T cells are commonly referred to as T-helper

(T_H) cells and provide assistance in activation of B cells and macrophages. $CD8^+$ T cells are also known as cytotoxic T cells (CTL) and can directly kill infected cells. T_H cells also help mediate the CTL response.

Both CD4 and CD8 T cells can be subdivided into functional subsets classified as naïve, effector, memory, and regulatory cells. The subsets are typically classified by their cytokine production with several major subsets of $CD4^+$ cells having been clearly identified to include T_H1, T_H2, T_H17, and regulatory T cells (T_{REG}) (31-35). T_H1 cells are associated with cell-mediated immunity (i.e. inflammatory response and cytotoxicity) and T_H2 cells with humoral immunity. Both cell types have relatively distinct cytokine production patterns with T_H1 cells producing IFN-γ, and IL-2 and T_H2 cells secreting IL-4, IL-5, IL-10, and IL-13 (33, 34). Additionally, these subsets are capable of downregulating each other with IFN-γ inhibiting the differentiation of T_H2 cells and IL-4 and IL-10 inhibiting T_H1 cell development (33, 36). T_H17 cells are a distinct cell line that can generate inflammatory reactions through secretion of IL-17 (37). Regulatory T cells have the ability to suppress a variety of immune responses, including T_H1 and T_H2 cell differentiation, largely through secretion of IL-10 and transforming growth factor (TGF)-β (36, 38). While an in-depth discussion of the mechanisms of actions for each functional cell subset is beyond the scope of this review, it is important to note that each subset has the ability to regulate the immune response as a result of their specific cytokine profile.

2.2.5 T Cell Activation: the Immune Synapse

When mature T cells are exposed to a target antigen, it initiates a complex process of proliferation and differentiation critical for a proper immune response. This process begins when T cell receptors (TCR) bind peptides on antigen-presenting cells (APC) and form the

immunological synapse (39, 40). Initial TCR-antigen binding forms TCR microclusters composed of 30-300 TCR at the primary contact area (41, 42) and increase in number as contact regions increase. Once a maximal number of contact points have been established, these microclusters migrate to the center of the cell-cell interaction to form a central-supramolecular activation cluster (c-SMAC) (39, 40). The c-SMAC is protected and supported by peripheral-SMAC (p-SMAC), leading to the characteristic "bulls-eye" structure of the immunological synapse that provides for a stable junction between the T cell and APC (40, 43).

Optimal T cell activation requires a two-signal process. The first signal is engagement of the TCR-CD3 complex to mediate activation of numerous downstream signaling proteins (44). This engagement forms a temporary association between the surface marker CD4 and leukocyte-specific tyrosine kinase (Lck) (40, 45). The association causes the phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAM) of the CD3 δ–, γ–, ε-, and ζ-chains (43). Phosphorylated CD3 ITAM results in TCR translocation of the 70 kDa zeta-activated protein (ZAP-70), which phosphorylates multiple tyrosines in the linker domain, resulting in the activation of T cells (LAT) (46). When phosphorylated, the LAT provides an assembly platform base for the inner leaflet of the plasma membrane and recruits important scaffolding proteins (SLP-76, Grb2, Gads) (43) and kinases such as IL-2 tyrosine kinase (Itk), phospholipase C γ1 (PLCγ1) and phosphatydilinositol-3 kinase (PI3K) (47, 48).

The second, or costimulatory, signal is the classical binding of a T cell CD28 receptor with an APC-bound B7-1 or B7-2 (43). Binding of CD28 in this manner leads to phosphorylation of tyrosine sequences in the cytoplasmic portion of the receptor. Additional phosphorylation furthers recruitment of downstream adapter proteins, such as PI3K and ITK, and expedites T cell activation (49).

The end product of TCR stimulation is transcription of the IL-2 gene, which has a primary role in supporting T cell proliferation (50, 51), and other cytokines that lead to cell differentiation and proliferation. This is facilitated by activator protein 1, nuclear factor of activated T cells (NFAT) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) (40, 43). Substantial amounts of clonal expansion are required for T cells to differentiate and mount an effective immune response. Accordingly, it is imperative that signal transduction occurring at the level of TCR microclusters and the immunological synapse occur without complication.

2.2.6 Lymphocyte Proliferation

Upon encountering a target antigen, T cells must go through clonal expansion to increase the number of lymphocytes to defend the host from the threat (11). IL-2 induction has been investigated as a crucial point of T cell proliferation (50, 51). IL-2 is a principal growth factor for T cells and maintains activated T cells in the proliferative cycle (19, 20). In steady-state conditions, IL-2 is mainly produced by T_H secondary lymphoid organs such as the lymph nodes (21, 52). Following activation by antigen, IL-2 and the IL-2 receptor (IL-2R), production is increased by $CD4^+$ and $CD8^+$ T cells (52, 53).

IL-2 binds to cells expressing either the high-affinity (trimeric) or low-affinity (dimeric) IL-2R (53). The low-affinity receptor consists of a common γ-chain cytokine receptor composed of CD122 and CD132. This dimeric complex has a weak affinity for IL-2 and needs to be expressed at a high level for sufficient ligand sensitivity. The trimeric form of IL-2R includes CD25, resulting in an increase in ligand binding affinity by 10-100 fold (53). CD25 expression on T cells is increased following TCR stimulation and also through a positive feedback loop

involving IL-2 (21). CD122 and the common cytokine receptor γ-chain are the signaling components of the quaternary IL-2/IL-2R complex with signal transduction occurring via several pathways including the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, PI3K/AKT pathway and the mitogen activated protein kinase (MAPK) pathway (21, 52, 54).

Lymphocyte proliferation can also be induced by factors other than cognate antigen. Plant lectins are carbohydrate-binding glycoproteins that agglutinate cells (55). When added to a cell culture, lectins act as a mitogen to induce lymphocyte proliferation similarly to lymphocytes that have been stimulated by an antigen (56). Mitogens, however, will activate a large percentage of cells regardless of antigen specificity and are referred to as polyclonal activators (57).

The primary mitogens used for proliferative assays [phytohaemagglutinin (PHA), concanavalin A (ConA), pokeweed mitogen (PWM)] work through distinct mechanisms to stimulate different subsets of lymphocytes. PHA primarily acts as a T cell mitogen (58) and is considered a valid inducer of T cell proliferation as only a small percentage of B cells are concomitantly stimulated (57). ConA can stimulate both B and T cells (58) and may accurately describe total lymphocyte proliferation while PWM primarily induces proliferation of B cell mitogen (58). The different stimulating properties of the mitogens effectively dictate what lymphocytes are being activated and how study results should be interpreted.

2.3 Neuroendocrine modulation of the immune system

The biological response to stress is to maintain systemic homeostasis while simultaneously reacting to a physical or psychological stressor. This highly conserved response, also known as “fight or flight”, is a function of two neuroendocrine responses: a fast, CNS-

driven adrenergic response by the sympathetic nervous system, and a parallel, but slower, response from the hypothalamic-pituitary-adrenal (HPA) axis. The sympathetic response occurs in a matter of seconds and manifests as increased heart rate (HR), blood pressure, and other physiologic responses that provide the body with resources to fight or flee (59). The HPA response begins with the release of corticotrophin releasing factor (CRF) from the hypothalamus (60). The release of CRF prompts the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, stimulating the release of glucocorticoids (GC) from the adrenal cortex. GC release results in the production of cortisol, a major hormone associated with stress and long-duration exercise, from the adrenal glands (61). Systemic increases in cortisol lead to elevated blood sugar and free triglycerides while also interacting with the immune response (62). This chain of events occurs over a matter of minutes and GC function as their own negative feedback mechanism, suppressing the HPA axis (63).

2.3.1 Sympathoadrenal Activation and Immune Function

Epinephrine (EPI) and norepinephrine (NE) are catecholamines released by the sympathetic nervous system that modulate immune cell activities such as cell trafficking and proliferation (64). EPI, which is released mainly by the adrenal glands, has been shown to produce dose-dependent increases in HR, ventilation and sweating during exercise while increasing blood flow to exercising muscles (59). NE, which is mainly released from postganglionic fibers in both target organs and the blood stream, has also been shown to redistribute blood flow to working muscles during exercise (65). The magnitude of the catecholamine response is determined through the combination of exercise intensity and duration (66).

Increases in catecholamines are observable within 30-60s after the initiation of high-intensity exercise (67). Increased concentrations of plasma NE occur during exercise intensities greater than 50% VO_{2max} (66) while EPI concentrations tend to occur at intensities $\geq$60% VO_{2max} (68). Both NE and EPI concentrations will peak at the end of exercise and return to baseline values within 20-30 min (69). The continued production of the catecholamines is necessary for their post-exercise immune function as free-circulating catecholamines are quickly degraded by either monoamine oxidase or catechol-O-methyltransferase, leading to a relatively short half-life of approximately 2-3min (70).

The magnitude of the total catecholamine response appears to be mediated by fitness level. Endurance trained subjects have reduced responses compared to untrained individuals at sub-maximal exercise intensities (71, 72). However, at maximal work intensities, well-trained individuals have a greater capacity for total catecholamine secretion compared to untrained individuals (73). It is unclear if long-term exercise training has any effect on baseline catecholamine concentrations (74).

The increased catecholamine concentrations after exercise correspond to a redistribution of inflammatory cells in the peripheral circulation (8-10). One of the principal characteristics of exercise is the increase of mononuclear cells in the blood, termed leukocytosis (10, 75). Neutrophil concentrations increase during exercise and continue to increase during the recovery period (8). Concentrations of natural killer (NK) cells and total lymphocytes increase quickly during exercise and fall below baseline values during the recovery period (8-10, 75, 76). Of the lymphocytes, NK cells show the greatest increases in concentration followed by $CD8^+$ and $CD4^+$ T cells (10, 77). NK cell counts can increase anywhere from 150-500% during or after high-intensity exercise and are the strongest contributor to exercise induced lymphocytosis (78, 79).

This increase is noteworthy as NK cells account for only 10-15% of resting peripheral blood mononuclear cells but 20-30% during exercise (75). Concentrations of circulating T cells increase during exercise with a greater percentage of increase in $CD8^+$ (50-100%) cells relative to $CD4^+$ (40-50%) (77). The differential mobilization of T cells leads to a decline in the CD4:CD8 ratio during exercise. The ratio of $CD4^+$ to $CD8^+$ cells in a healthy person is approximately 2:1 (80). An inverted ratio between these cells is associated with viral infections or other impairments in immunocompetence (81). In regards to exercise, changes in this ratio are likely a result of the increased mobilization of $CD8^+$ cells. $CD19^+$ B cells exhibit moderate to no change in cell counts during exercise (76, 82).

Catecholamine receptors are present on lymphocytes and leukocytes and are thought to be involved in altering immune cell distributions during stress (83, 84). Adrenergic β_2-receptors (β_2-r) primarily influence lymphocytes (85) while neutrophils are regulated by adrenergic α-receptors (α-r) (7). NK cells have the highest density of β_2-r followed by $CD8^+$ and $CD4^+$ cells, respectively (86, 87). Spikes in circulating EPI and NE seen during acute stress and exercise are associated with quick redistributions of granulocytes in circulation (6, 7). *In vivo* expression of β_2-r on T and B cells have been shown to increase post-exercise and return to baseline levels after 30 min of recovery (88). Interestingly, an association has been shown between density of β_2-r on lymphocyte subsets and cell trafficking patterns ($NK>CD8^+>CD4^+$) following stress and/or exercise (87), suggesting that the role in inflammatory trafficking during exercise is controlled, at least partially, by β_2-r. Furthermore, administration of physiological doses of EPI in human subjects has been shown to accurately mimic this leukocyte response to exercise (89).

Stimulation of β_2-r inhibits T cell proliferation (90) and down regulates IL-2R (91). Decreases in IL-2 secretion by T cells have been linked to increased intracellular levels of cyclic-

AMP (cAMP), providing a mechanism in which β_2-r may regulate T cell proliferative capacity (92, 93). This is supported by evidence in which the proliferative response of $CD8^+$ T cells was diminished compared to $CD4^+$ cells, likely due to the increased density of β_2-r on $CD8^+$ cells. (92, 94).

2.3.2 Hypothalamic-Pituitary-Adrenal Axis and Immune Function

Changes in circulating GC concentrations in response to exercise are similar to the catecholamine response and depend on exercise intensity and duration, even though cortisol has a half-life of close to an hour, compared to 2-3 min half-life of the catecholamines (95). Cortisol concentrations increase at exercise intensities $\geq$60% VO_{2max} or during exercise lasting longer than 1 h (69). Conversely, the same study reports concentrations may decrease during low intensity exercise ($\leq$50% VO_{2max}) (69). Cortisol levels begin to increase after 10 min of high-intensity exercise and peak around 20 min after exercise ends (96).

GC are considered to be immunosuppressive in terms of both cell trafficking (97) and proliferation (98). GC reduce the number of eosinophils (99) and basophils (100) in circulation while increasing the number of neutrophils and facilitating opsonization and phagocytic processes (101, 102). In contrast to the catecholamine response, which recruits lymphocytes from the periphery, GC secretion may facilitate an egress of lymphocytes out of the peripheral circulation (1, 103). Cortisol concentrations have been directly correlated with circulating neutrophil counts but inversely correlated with lymphocyte and eosinophil numbers in blood serum taken immediately after a marathon race (104, 105). This finding is not uniform as other studies have found no significant relationship (106, 107) or conflicting results following an

exercise stimulus (76, 108-110), although a limitations in these latter studies are non-uniform exercise bouts.

The anti-proliferative effects of GC on lymphocytes appear to be mediated through the inhibition of IFN-γ, IL-2, and IL-12 (98, 111), with evidence suggesting that a major component is dysregulation NFκB signaling and decreased transcription of IL-2 (112). Determining the mechanistic processes in the dysregulation is difficult due to redundant inflammatory pathways and protein signaling "cross-talk".

As GC concentrations tend to peak later than catecholamines, it has been hypothesized that cortisol serves to maintain increased numbers of circulating neutrophils and signal for lymphocytes to exit the peripheral circulation following exercise (113). Schedlowski et al (103) provide compelling evidence supporting this hypothesis after examining lymphocyte trafficking and plasma hormone concentrations in parachutists. The study observed a significant increase in total T cell and NK cell counts immediately after the jump but a decrease to below baseline values at 1 h post-jump. The observed lymphocytosis was associated with increases in circulating catecholamines whereas the lymphopenia (clearing of peripheral lymphocytes) was inversely correlated with plasma cortisol concentrations (103).

The biphasic hormone response represented by the relative increases in hormones of the sympathoadrenal and HPA axes most likely have differential effects on immune cell trafficking and function. This requires investigators to account for the combined effects of both catecholamines and GC when assessing the immune response following exercise or stress.

2.4 Cytokines

Cytokines are a diverse family of small glycoproteins that modulate many physiological processes but are highly relevant in controlling the intensity and duration of inflammatory responses. These peptides are often effective at small concentrations and can act in autocrine, paracrine, intracrine (within the same cell), or endocrine fashions. Cytokines are readily produced and secreted by endothelial cells, smooth muscle cells, fibroblasts, skeletal muscle, adipose tissue, and virtually all immune cells (114, 115). Cytokines often exhibit pleiotropic and redundant properties and can interact with other cytokines in antagonistic or synergistic capacities (114). The actions of cytokines are quickly induced following cellular activation as various feedback mechanisms rapidly regulate cytokine uptake and utilization (116). The aim of this section is to address cytokines important to functional T cell subsets following exercise.

The cytokine profiles of T_H1 and T_H2 cells are of interest due to their roles in moderating different components of the adaptive immune response. T_H1 cells primarily secrete the pro-inflammatory cytokines IFN-γ, IL-2, and IL-12, which are involved in facilitating cell-mediated immunity and delayed-type hypersensitivity (a secondary immune response appearing 48-72 hr after exposure to antigen). The T_H1 cytokines also activate macrophages and NK cells, with IL-2 specifically involved in proliferation of $CD4^+$ and $CD8^+$ T cells.

IL-4, IL-5, and IL-10 are derived primarily from T_H2 cells and mediate humoral immunity. The cytokine profiles of Th1 and Th2 cells are interesting as they inhibit the function of each other. This is best observed in Th1-derived IFN-γ inhibiting Th2 and Th2-derived IL-10 inhibiting T_H1 cells. This cross-regulation is also observed at the level of IFN-γ which can be inhibited by IL-10 and upregulated by IL-12 (117). Cytokine concentrations in the microenvironment drive cell differentiation as well with IL-4 being a potent stimulus for

differentiation into a $T_H2$cell and IL-12, and IFN-γ leading to T_H1 cell development (118). The overall relationship between T cell and cytokine regulation can be seen below in Fig. 1.

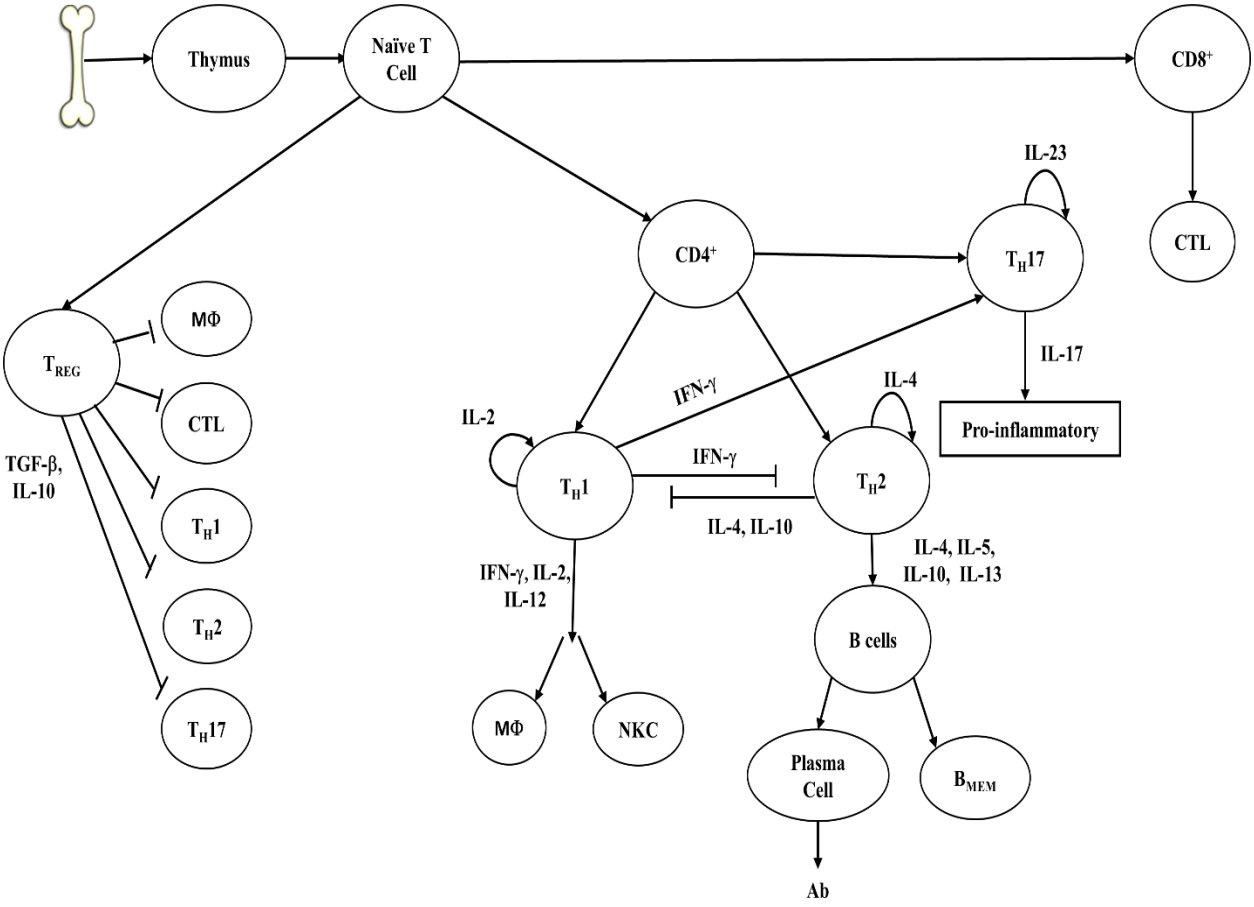

Fig. 1. Simplified diagram of cytokine interface with T cells. Cytokines are secreted by T cells with inhibitory and cross-regulatory effects. Arrowed lines indicate a stimulus in favor of differentiation/activation. Blocked lines indicate an inhibitory effect. MΦ = macrophage; Ab = antibody.

2.4.1 T_H1 Cytokines and Exercise

Exercise likely has a role in altering the concentrations of principal effector cytokines from T_H1 cells in the serum. Although no studies have observed increases of IFN-γ following acute exercise *in vivo*, studies examining *ex vivo* production of IFN-γ report decreased concentrations after acute bouts of exercise after isolation of peripheral blood monocytes and

lymphocytes and whole blood (119-121). This is not unexpected as IFN-γ production is suppressed by catecholamines and cortisol (122-124), which increase following exercise.

Accumulated evidence suggests IL-12, which induces the release of IFN-γ from T_H1 cells, does not increase following exercise (125, 126). Conversely, Rhind, *et al*. (127) observed increases following exercise in the heat (cycling at 65% VO_{2max} for 40 min at 39˚C) although the observed changes were at concentrations ≤ 5 pg/ml and may not be physiologically relevant. One study investigating responses to maximal exercise using a modified Wingate protocol did find significant increases in IL-12 (128).

Plasma IL-2 concentrations have largely been shown to decrease or remain unchanged during exercise (115). Recently, however, Kakanis, *et al*. (129) found increased concentrations of IL-2 4-8 h after a 2 h bout of cycling at 90% of the subjects' anaerobic threshold. This result may be indicative of T cell activation and suggests that previous investigations may have collected data at the wrong time points. Accordingly, future research should sample multiple time points to allow for the immune response to develop following exercise.

2.4.2 T_H2 Cytokines and Exercise

The IL-4 response to exercise is inconsistent within the literature and suggests circulating concentrations are largely unchanged following acute bouts of exercise (115, 130). Della Gatta, *et al*. (131) recently observed that while IL-4 either does not change, or may decrease following an acute bout of resistance exercise in untrained individuals after three months of supervised resistance training 3 times a week those same subjects reported increased IL-4 concentrations after an acute bout of exercise, indicating training status may affect the IL-4 response.

There is little data for exercise effects on the secretion of IL-5. Chan *et al*. (132) looked at the role of carbohydrate supplementation and the IL-5 response to exercise. They found a resistance exercise session consisting of 5x10 back squats at 65% 1RM and 3x10 half squats at 85% 1RM, with each set having 1 min rest interval, led to decreased post-exercise IL-5 concentrations of 12% in the subjects given carbohydrate and 26% in those given placebo. This may indicate that carbohydrate supplementation minimizes the IL-5 response.

Circulating concentrations of IL-10 have consistently shown increases following exhaustive endurance exercise (115). Studies investigating short duration, high-intensity have had mixed results with some studies seeing significant elevations in IL-10 immediately post-exercise (133) while others see a time delayed response (134). For example, Smith, *et al*. (134) observed significant elevations in IL-10 at 72 h, 96 h and 144 h post-exercise following a high-intensity, eccentric loading protocol (4x12 eccentric bench press and leg extension with 2 min rest) which may be indicative of a delayed anti-inflammatory response following short duration, high-intensity events.

2.5 Exercise Immunology

Exercise-associated lymphocytosis and lymphocytopenia have been reported on extensively (8-10) and suggests the characteristic immune response to exercise involves an increase in lymphocytes mobilized from the marginal pools in the blood and other organs. This is followed by a decrease to below baseline levels as the mobilized cells move into areas like the skin, mucosa, and lymph nodes. These findings have produced ideas like the "Open Window" hypothesis whereby individuals are thought to have decreased immune function following intense physical activity. Epidemiological studies seem to support this as athletes participating in

sustained periods of high-intensity exercise are at increased risk for opportunistic infections (i.e. upper respiratory tract infection [URTI; (8, 135)]. The risk of infection in those that exercise follows a 'J' curve (Fig.2) with regular, moderate-intensity exercise improving immune function and sustained high-intensity exercise increasing risk of infection (136, 137). Efforts to identify how exercise intensity modulates immune function have largely focused on lymphocyte trafficking following exercise, which contribute little information about the overall functional capacity of a lymphocyte, termed immunocompetence, of an individual (8, 136).

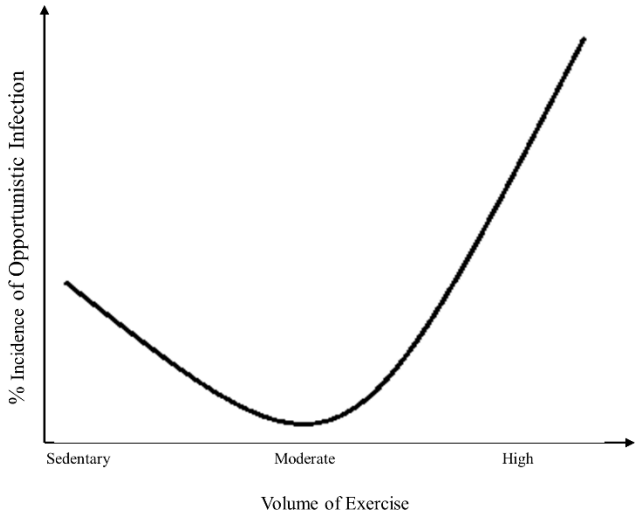

Fig. 2. The risk of infection relative to volume of exercise. Adapted from Nieman, *et al*. (1994)

A better method of determining immunocompetence is investigating the proliferative ability of lymphocytes in response to cognate antigen. Lymphocytes undergo clonal expansion when they encounter cognate antigen (11) and this is a critical feature of the adaptive immune response (12). Any failure to proliferate in response to a foreign antigen is indicative of impaired immune function and attenuates the immune response of the host. The classical assay to measure T cell proliferation is to stimulate them with PHA, a T cell-specific mitogen. PHA assays are routinely used to monitor immune function in immunosuppressed patients such as recipients of organ transplants, individuals that are HIV-positive, and others at risk for immunosuppression.

Although proliferation assays are a mainstay of clinical diagnostics, they represent a small proportion of the literature comprising the field of exercise immunology (9, 138).

2.5.1 Lymphocyte Proliferation Following Exercise

Non-systematic review articles of lymphocyte proliferation report inconsistent findings regarding whether immune function is enhanced or suppressed by exercise [see reviews in (8-10, 138)]. These inconsistencies are likely a result of varied subject populations, different exercise protocols and methods that evaluate lymphocyte proliferation. A systematic review of published studies involving measurements of lymphocyte proliferation immediately after acute exercise suggests that exercise does indeed suppress lymphocyte proliferation (ES: -.22, 95% CI:-.29, -.24; Siedlik, *et al*. Unpublished Data). Follow up analyses in this same study found no appreciable differences between exercise of moderate and high intensity (ES = -0.17 vs. -0.27 respectively), but did uncover a trend for a suppressive effect of long duration (≥60min) exercise relative to short-duration (<60 min) (Fig. 3).

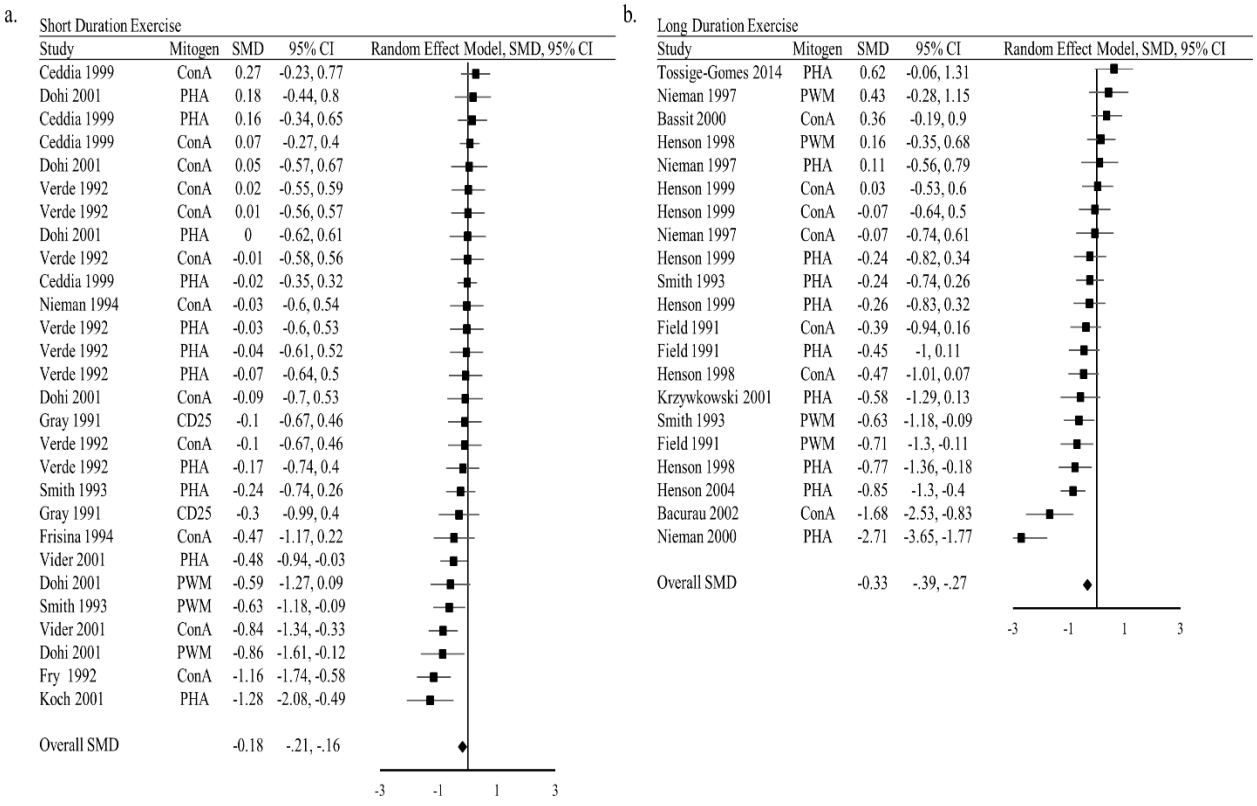

Fig. 3. Effect of short duration (a) and long duration (b) exercise on measures of lymphocyte proliferative capacity. Data are presented as mean effect size (boxes) for each study, 95% confidence intervals (horizontal lines), and summary of overall proliferative effect (diamonds).

While there was no statistically significant difference in suppression based on duration of exercise, there was a differential response for exercise intensity with long duration high-intensity exercise having a greater suppressive effect than long duration moderate-intensity (-0.55 vs. -0.24; Fig. 4). Beyond the quantification of acute exercise-induced proliferative responses, the systematic review identified two different responses within the context of high-intensity exercise lasting longer than one hour. The first response is a greater suppressive effect following high intensity training intervals lasting over two hours and the second being enhanced proliferation following competitive events (Siedlik, *et al*. Unpublished Data).

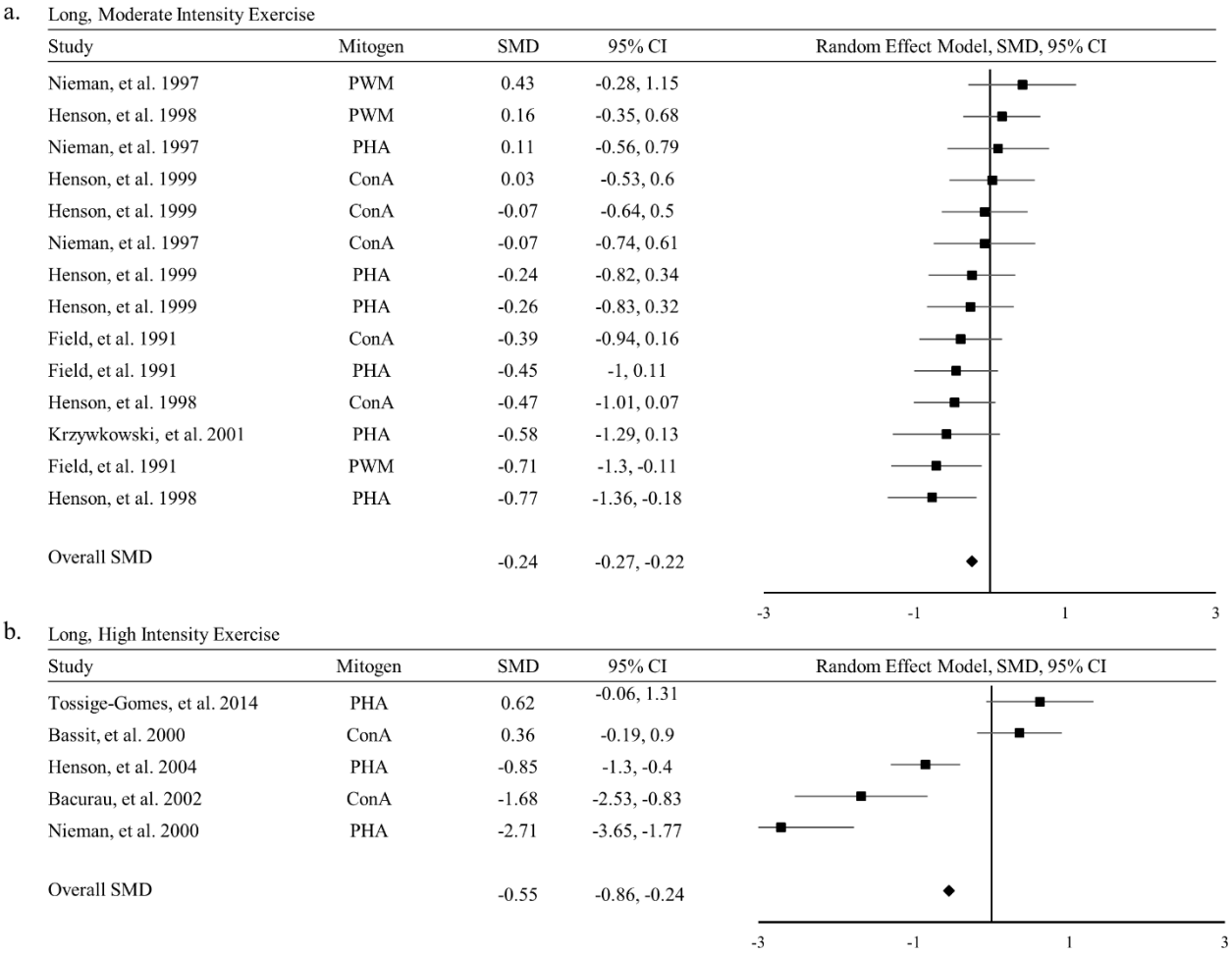

Fig. 4. Effect of long, moderate-intensity (a) and long, high-intensity (b) exercise on measures of lymphocyte proliferative capacity. Data are presented as mean effect size (boxes) for each study, 95% confidence intervals (horizontal lines), and summary of overall proliferative effect (diamonds).

Two articles used in the comprehensive review had very large effect sizes due to their unique study designs. Bacurau *et al*. (139) investigated the immune response in trained cyclists participating in an exercise bout composed of cycling intervals (6x20 min with equal rest intervals) at 90% of their anaerobic threshold. Additionally, Nieman *et al*. (140) examined the proliferative responses of elite adolescent tennis athletes who maintained a mean HR of over 80% of their predicted HR_{max} throughout 2 h of high-intensity tennis drills performed in 15 min intervals with 4-5 min rest. While these studies have work intervals greater than 60 min, they also had a higher sustained intensity level and their large changes in the proliferative response

may be unique to high intensity, long-duration activity. Thus, the data suggest an enhanced suppressive effect following events of this nature that needs to be accounted for in research designs.

The proliferative capacity, however, may increase immediately after competition. Bassit, et al. (119) examined immune responses after a competition of an Olympic distance triathlon (1.5 km swim, 40 km bike, 10 km run) and noted an increase in lymphocyte proliferation immediately post-race. This is supported by a report that evaluated lymphocyte proliferation immediately after an Adventure Spring Race consisting of 12 km of hiking, 100 m of vertical skills, and 30 km of mountain biking (141). These studies contrast to the observed effects from long duration, high-intensity exercise in a non-competitive setting and suggest that the psychological stress unique to competition may regulate the immune response via a different mechanism (Fig. 3). To further clarify this we conducted a sub group analysis examining whether the proliferative response to competition differed. We did identify a discordant result ($p=0.02$) with the long duration, high intensity competitive events being associated with an enhanced proliferative effect (SMD): 0.46, 95% CI: 0.03, 0.89) and long duration, high-intensity exercise outside of a competition having a large suppressive effect (SMD: -1.28, 95% CI: -1.61, -0.96; Siedlik, *et al*. Unpublished Data). It should be noted that Henson, *et al*. (142) was included as a long duration, high-intensity event but not a competitive one as the average finish time was 4.57 h which suggests the participants were mainly recreational runners.

The reason for the observed differences in proliferative responses in unclear at this time. It is known that exercise, particularly exercise of long duration, leads to increased circulating concentrations of hormones and cytokines that may modulate the immune response. Radom-Aizik, *et al*. (143) observed that Jurkat cells, an immortalized T cell line, exhibited increased

proliferative ability following stimulation by proliferating nuclear cell antigen when treated with sera obtained from healthy donors following a bout of exercise (30 min cycling at 80% peak work rate). This supports the hypothesis that serum factors are able to modulate T cell function *in vitro*, and suggests that secreted soluble factors are at least partially accountable for changes in immunocompetence following exercise. The identification of these secretory factors and their mechanisms of action for the immunomodulatory responses has not yet been elucidated.

2.5.2 Effect of Fitness

Training status is likely another factor involved in the immune response to exercise. Few studies have attempted to quantify differences between trained and untrained subjects. In those that have, mixed results have been reported when comparing trained versus untrained subjects with studies finding trained individuals have either increased, decreased, or no change relative to untrained individuals of similar age.

A study by Baj, *et al*. (144) examined competitive cyclists before and after a training season (6 months) and found that proliferative capacity at rest was improved following the intensive training/racing season and that those changes were associated with increases maximal oxygen consumption. Nieman, *et al*. (145) found a similar result with well-conditioned (actively competing in endurance events) elderly women exhibiting greater proliferative ability compared to age matched sedentary controls.

Papa, *et al*. (146) found decreased proliferative ability in trained water polo players compared to untrained volunteers. PHA and PWM were used as mitogens in this study looking at responses in a rested condition, with proliferation decreased for both measures in the trained group.

Potteiger, *et al*. (147) undertook an elegant study examining the functional immune response to an acute bout of exercise in resistance-trained versus untrained-females. This study found that trained females (3 d/wk resistance training for at least 3 months prior to study start) did not see a significant reduction in T cell proliferative capacity after a bout of resistance exercise while untrained females exhibited suppressed proliferative ability up to 3 h post-exercise. These data suggest high-intensity resistance training may influence T cell proliferative capacity following an exercise bout and that differences in training backgrounds may be a confounding variable and should be better controlled for in future studies.

Other studies have found no difference in proliferative capacity between trained individuals and age matched controls. Oshida, *et al*. (148) found parallel suppressive effects immediately post-exercise in both untrained individuals and athletes (~20 km running, 6-7 d/wk) with no appreciable difference between groups. Similar results have been found in studies comparing resting levels of lymphocyte proliferative ability in athletes and non-athletes (VO_{2max}: 70.7 ± 1.3 vs. 47.6 ± 3.1) (149) and in marathon runners (minimum 4 y training/racing marathons) relative to sedentary controls (150).

The major limitation of these studies, and the field of exercise immunology, is a non-universal classification of a trained individual. In the literature, trained status often ranges from recreational to elite and researchers may not explicitly state how they qualified their subjects' training status. One can appreciate that there may be substantial variances in the outcomes due to these inconsistencies.

2.5.3 Mitogen Selection and Methodical Limitations

The primary mitogens used for proliferative assays (PHA, ConA and PWM) work through functionally distinct mechanisms and allow for the stimulation and measurement of different subsets of lymphocytes. Pooled measurements, which combine studies using multiple mitogens into a single analysis, give an accurate representation of total proliferative capacity, but do not allow for a discussion regarding specific mechanisms of exercise-derived immunosuppression. As an example, the overall SMD in global suppressive effects of acute exercise observed in studies that used both PHA and ConA is trivial (-0.15 and -0.09 respectively; Fig. 5). In Fig 5 all studies that used both PHA (5a) and ConA (5b) in the systematic review are listed and sorted according to effect size from largest to smallest. Note that while the overall SMD are very similar, the individual SMD differences between PHA and ConA are different even though the subjects and exercise stimuli are identical. These observations suggest a lack of agreement between variable measures, which is likely a result of the different mitogenic properties, and confounds our understanding of the immune response to acute bouts of exercise.

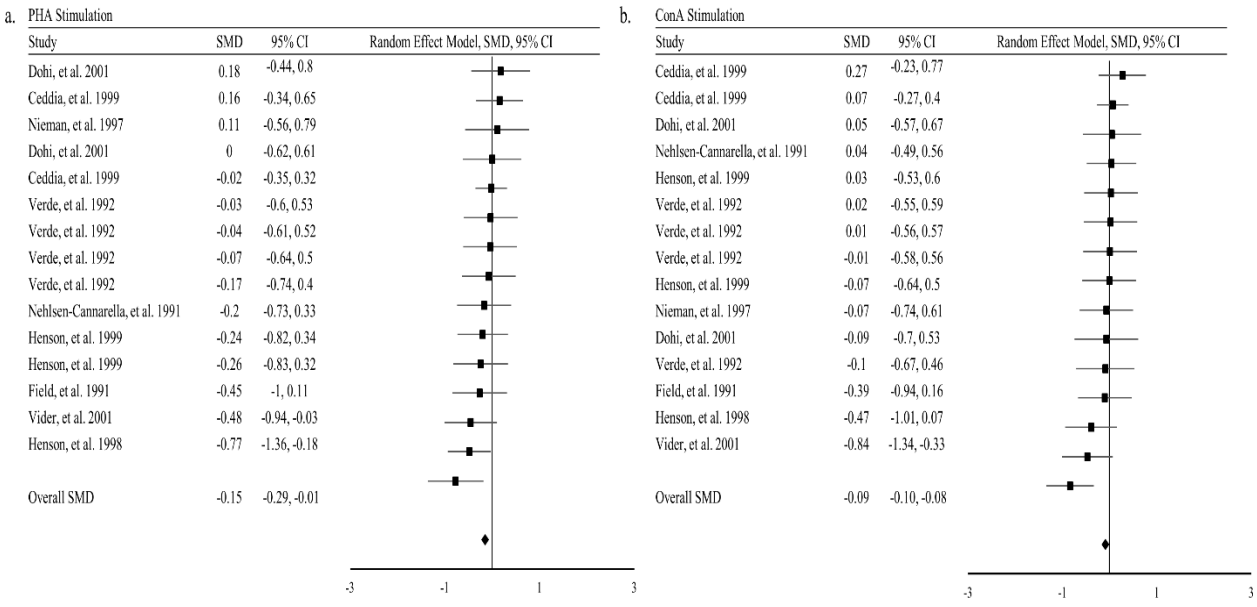

Fig. 5. Lymphocyte proliferation following stimulation by either Phytohaemagglutinin (a) or Concanavalin A (b) stimulation following an acute bout of exercise. Data are presented as mean effect size (boxes) for each study, 95% confidence intervals (horizontal lines), and summary of overall proliferative effect (diamonds).

While Fig. 5 allows for a direct comparison of effects, other studies that do not use both PHA and ConA limit the ability to compare results across study designs. Mitogen-specific suppression of long duration exercise provides an estimated SMD = -0.46 (95% CI: -0.56, -0.35) for PHA and a SMD = -0.21 (95% CI: -0.31, -0.12) for ConA (Siedlik, *et al*. Unpublished Data). This difference in estimated SMD, while not statistically significant, suggests a suppressive mechanism may be preferentially targeting the T cell compartment during exercise lasting greater than 60 min. We suggest that PHA is a more accurate assessment of T cell proliferation and research investigating proliferative responses to exercise should consider the mitogenic properties of possible lectins and target lymphocyte subsets. This is supported by existing literature (57, 58, 151, 152) and in agreement with clinical immunology practices.

The question of which lymphocyte subpopulation is being activated is further complicated by cell culture techniques utilized for proliferation assays. The majority of studies

use either peripheral blood mononuclear cells or whole blood cell. These may limit functional capacity measurements of specific cell type functional unless a cell specific mitogen (i.e. PHA) is utilized. For this reason, interpreting data pairing culture methods using ConA or PWM, both of which can activate B cells, must be done carefully.

It has been argued that whole blood assays accurately represent *in vivo* conditions and are the best method in assessing proliferative responses (153). The primary concern with this method is the combination of lymphocytes, leukocytes, and immunomodulatory factors such as cytokines and hormones present in the blood, limit mechanistic analyses of proliferative capacity and make difficult the ability to measure a specific lymphocyte's function in this manner. Peripheral blood mononuclear cell assays, on the other hand, isolate white blood cells for analysis but cannot differentiate between T and B cell responses. For these reasons, it is difficult to draw conclusions for clinical implications of these findings as they relate to increased risk of infection.

2.6 Dual Stress Challenges

As mentioned previously, it is generally accepted that a single exposure to a physical or psychological stress can lead to increased concentrations of catecholamines and GC and a resultant suppression of immune function. A meta-analysis examining the impact of psychological stress on immune parameters found increased numbers of circulating leukocytes and lymphocytes following mental challenges to a degree similar to acute physical stress (154). The same study found a decrease in mitogen-induced lymphocyte proliferation following timed events associated with psychological stress, such as public speaking and mental arithmetic, and this data is suggestive of a functional impairment in adaptive immunity (154). Stressful life events have also been linked to increased risk of viral respiratory infections in a dose-dependent

manner (155), further solidifying the current opinion that stressful encounters compromise immune function.

It should be noted that in the everyday environment it is exceedingly rare for an individual to be exposed to *only* a physical or psychological challenge and there are a variety of ways individuals experience multifactorial stressors in practical scenarios. This can be seen in conditions where performers may experience state anxiety. Elevations in endocrine measures specific to a stress response have been observed in judoka (156) and ballroom dancers (157) prior to a competition when compared to these same individuals' response to a time-matched training session. These results, which are anticipated to occur, represent a potential confounding variable in studies where participants are placed in anxiety-arousing situations due to the nature of the task they are asked to complete.

Recent studies have compared paired physical & psychological dual stress models to physical stress alone (i.e. a bout of exercise) and have observed increased concentrations of circulating catecholamines and cortisol (16, 158) in the dual-challenge groups compared to the exercise only controls. Descriptive studies have reported the catecholamine responses in veteran firefighters undergoing laboratory based exercise alone (37 min cycling at 60% VO_{2max}) and during dual stress conditions. These participants were subjected to the same exercise condition but underwent a 20 min computer based firefighting strategies and tactics decision-making challenge during minutes 12-32 of the exercise trial (13-15). These studies have repeatedly observed increased concentrations of EPI and NE relative to the exercise-alone controls (13-15) and are suggestive of greater sympathetic activation resulting from the combined challenge paradigm.

Increased activation of the HPA axis was also observed during one of the above referenced studies (15) but was not assessed in the other two (13, 14). Webb, *et al*. (16) utilized the same exercise stress (37 min cycling at 60% VO_{2max}) but had civilian subjects undergo five consecutive cycles of a modified Stroop Color-Word task and mental arithmetic challenge during minutes 12-32 of the exercise protocol. They observed a resultant increase in circulating cortisol levels in the dual stress challenge compared to the exercise alone condition. In another study, Webb, *et al*. (158) found that a mental task (20 min of cycled Stroop Color-Word and mental arithmetic tasks) preceding 20 min of cycling at 35% VO_{2max} enhanced the cortisol response to exercise above what would be expected from exercise at such a low intensity. The mechanism(s) for these types of exacerbated endocrine responses are unknown but indicate there may be a synergistic interaction in the multifactorial stress response.

In an effort to examine immune responses in this context, Huang *et al*. investigated the response of veteran firefighters to combined physical and psychological stressors and identified a greater increase of EPI, NE, and IL-2 in the dual challenge condition when compared to an exercise-alone trial (14). The same authors expanded their inquiry into the civilian population but did not observe increased concentrations of IL-2 (159). Although the results are seemingly contradictory the primary factor driving this disparity is most likely baseline aerobic fitness levels as the firefighters had roughly a 20% greater VO_{2max} (45.13 ± 7.7 ml/kg/min) vs. the civilian subjects (36.9 ± 5.6 ml/kg/min) (14, 159).

Aerobic fitness has been thought to mitigate the cardiovascular response to psychological stress (160, 161). Rimmele, *et al*. (162) examined how the physiologic stress response is mediated based on levels of physical activity. Participants were separated into untrained (no running), amateur (~2.43 h/wk running), and elite (~4.67 h/wk running) groups. These

participants underwent the Trier Social Stress Test to induce psychosocial stress. They found runners in the elite group had reduced heart rate and cortisol responses to the psychosocial stressor when compared to both the amateur and untrained subjects (162). These researchers were able to further define a graded relationship between physical activity level and anxiety management. They demonstrated that the greatest reductions in the anxiety response (physiologic and psychological) occurred at the highest levels of physical activity (162, 163). These findings are supported by observations in which subjects with low aerobic fitness exhibit exacerbated cardiorespiratory (164) and cortisol responses (16) compared to aerobically fit individuals following dual stress conditions. This is supportive of a role for anxiety in altering stress markers independent of the physiological response while also leading to differential immune activation between fit and unfit individuals.

In a recent study attempting to assess immunoendocrine interactions in a real-world field testing environment during and after exposure to a dual stress intervention, Siedlik, *et al*. (165) testing aerobically fit male Marines using a standardized US Marine Corps Martial Arts Training protocol, a program encompassing training and teaching in a high-stress environment with constant feedback from senior officers, and found elevated circulating catecholamine concentrations and increases in circulating leukocytes and lymphocytes without activation of an adaptive immune response. Quantification of the functional immune response to combined stress challenges specific to real-world contexts can improve our understanding and development of wellness interventions for occupations that are consistently exposed to physical and psychological stress (i.e. firefighter, law enforcement, and military).

2.7 Conclusion

Lymphocyte proliferative ability is a crucial component of the adaptive immune response. Failure to proliferate in response to cognate antigen is indicative of impaired immunocompetence. The functional capacity of these cells, specifically T cells, is modulated by a variety of factors including changes in hormone and cytokine concentrations.

Exercise is a prominent way to activate and suppress lymphocyte function as the composition of the peripheral circulation changes in response to the exercise stimulus. These changes may be related to a convergence of interactions with soluble mediators generated by a physical stress, a psychological stress, or a combination of the two. Accordingly, the goal of the proposed studies is to illuminate how a physical stress such as exercise or a dual-stress challenge affects global measures of immunocompetence. Specifically, the aims are to investigate T cell proliferation and discern the discrete steps involved in T cell activation during multiple stress models.

Chapter 3: Methods

3.1 Study 1: T cell Activation Following Moderate Intensity Exercise

Subjects

Six healthy males volunteered for this study (age = 26 ± 5 yrs; height = 181 ± 9 cm; weight = 88 ± 14 kg). All subjects were recreationally trained individuals with a mix of aerobic and resistance training experience (average 1-mile run time: 5:58 ± 40 s; average 1-repetion maximum back squat: 167 ± 42 kg). The subjects' self-reported time spent aerobic training each week was 2.5 ± 2.2 h with an average of 4.2 ± 2.5 h resistance training. Subjects provided informed consent and completed a medical history questionnaire prior to participation. At the time of recruitment, subjects were instructed to maintain their normal dietary patterns prior to participating in either session but to refrain from exercise in the period 24 hrs before data collection. The study was approved by the Institutional Review Board for Human Subjects at the University of Kansas, Lawrence Campus.

Testing protocol

Subjects were tested on two occasions with each laboratory visit occurring between 0800-0845 hours. During the treatment visit, subjects underwent 30 min of moderate exercise comprised of 15 min of treadmill running followed by three times through a resistance training circuit. Each circuit consisted of 10 repetitions of the back squat at 135 lbs, as many repetitions as possible (AMAP) body weight pull-ups (max 25), and AMAP of body weight dips (max 25). Rating of Perceived Exertion (RPE) was measured every 3 min (time points included were 3, 6, 9, 12, and 15 min) during the treadmill portion with speed and grade adjusted to achieve/maintain an RPE of 15-16 on the 6-20 Borg Scale (166). Following the treadmill portion, subjects were given a 3 min rest break before beginning the first resistance training circuit.

Additional 3 min rest breaks were provided between each circuit with RPE assessed at the beginning of each rest period.

During the control visit, subjects sat quietly in a room for 30 min. Subjects were not allowed to read or use electronic devices during this time. Subjects were monitored at random intervals to ensure they remained awake.

Physiological monitoring

Participants were fitted with a Zephyr BioHarness 3 (Zephyr Technology, Annapolis, MD, USA) for heart rate (HR) measures. Continuous HR measures were recorded at 1 Hz intervals during the training session. HR data was downloaded using the Zephyr BioHarness Log Downloader (version 1.0.29.0). Five training zones were defined as follows: zone 1 <60% predicted maximum HR (HR_{max}); zone 2, 60%-70% HR_{max}; zone 3, 70%-80% HR_{max}; zone 4, 80%-90%; and zone 5, >90% HR_{max}. HR_{max} was estimated using the methods of Tanaka et al. (167).

Blood collections

Blood draws were performed by physician-approved allied health care providers using standard phlebotomy techniques. Venous blood samples were obtained by venipuncture of the antecubital fossa at baseline (Pre) and immediately post (Post) the testing sessions in sodium heparin Vacutainers.

Antibodies and reagents

All antibodies used for flow cytometry were purchased from BioLegend (San Diego, CA) and include: anti-CD3-APC, anti-CD4-APC, and anti-CD25-PE. Cells were stained with 2.0 μM

5-(and-6)-carboxyfluorescein diacetate, succinimidyl ester (CFSE, BioLegend, San Diego, CA) on day 0 of stimulation for proliferation assays. Flow cytometry was performed using an Accuri C6 (BD Accuri Cytometers, Ann Arbor, MI) and data analysis using CFlow Plus (Accuri).

Cell purification and culture

Peripheral blood (30 ml into sodium heparin) was obtained at each time point for analyses of T cell proliferation. One pair of pre/post blood samples were processed immediately post exercise while the other two sets of blood samples were held overnight at room temperature or 4˚C. For all samples, total T cells were isolated from the peripheral blood by negative selection using a Human T cell enrichment kit (Stemcell Technologies, Vancouver, BC, Canada). Cells were cultured immediately at 37˚C with 5% CO2 in complete RPMI 1640 (Mediatech, Herndon, VA) containing 10% fetal bovine serum (Atlanta Biologicals, Lawrenceville, GA), 50 U/ml each of penicillin and streptomycin (Life Technologies, Grand Island, NY), and 20 mM L-glutamine (Life Technologies).

T cell stimulation

T cell proliferation was analyzed in response to co-stimulation through CD3+CD28 using either plate-bound antibodies, PHA treatment, or no simulation. Each antibody was titrated to the lowest concentration that gave maximum T cell proliferation: anti-CD3 (OKT3) was used at 1 μg/ml (BioLegend, San Diego, CA) and anti-CD28 (CD28.2) at 2 μg/ml (BioLegend, San Diego, CA). Antibodies were diluted to their indicated concentrations in sterile Dulbecco's PBS (dPBS; Life Technologies) and incubated in 96 well plates overnight at 4˚ C; unbound antibodies were removed by washing 3X with dPBS immediately before cell plating. Total T cells were plated at

1.5 x 10^6 cells/ml in 200 μl of complete RPMI 1640 directly after isolation. Stock 5 mg/ml PHA (Sigma-Aldrich, St. Louis, MO) was diluted into complete medium before use and added to appropriate wells immediately following cell plating to final concentration of 2.5 μg/mL. Cells were incubated for 7 d at 37˚ C in a humidified incubator with 5% CO_2 and then analyzed by flow cytometry

Statistical analysis

Data were analyzed using a three-way mixed factorial ANOVA (trial [control x exercise] x time [pre x post] x delay condition [immediate (SP) x 24hrs room temperature (RT) x 24hrs 4˚C (CH)]). When appropriate, follow-up analyses were performed using independent samples t-tests and ANOVA models with Bonferroni corrections. The level of significance was set at α = 0.05. All statistical analyses were performed using SPSS 22 (IBM Corporation, Armonk, New York, USA).

3.2 Study 2: Do Military and Tactical Experiences Model the Characteristic Exercise Response

Subjects

Sixteen healthy, recreationally trained males (aerobic and/or resistance exercise 3-5 d/wk) volunteered for this study. Participants were randomized to either a high-intensity (HI) (age = 21 ± 3 y; height = 178 ± 6 cm; weight = 82 ± 8 kg) or moderate-intensity (MOD) (age = 20 ± 1 y; height = 182 ± 9 cm; weight = 84 ± 6 kg) group after study enrollment. There were no statistically significant differences between subject demographics between groups. Participants reported no recent use of non-steroidal anti-inflammatory drugs (NSAID), aspirin, or other over-the-counter or prescription medications. Participants were instructed to refrain from exercise 24

h prior to data collection. This study was approved by the University of Kansas Institutional Review Board for Human Subjects at the University of Kansas, Lawrence, and all participants provided written informed consent and completed a Health & Exercise Status Questionnaire prior to participation.

Dietary Controls

To ensure participants consumed a consistent diet, both in terms of energy content and macronutrition, food intake was standardized during data collection. Participants were instructed to abstain from caffeine and alcohol 12 h prior to data collection and to report in an 8 h fasted state. Each individual consumed a meal of commercially available food bars (Clif Bar & Company) and shakes (CytoSport, Inc) 1 h prior to baseline blood collection. The meal contained 460 kcal, 17 g fat, 38 g carbohydrate, 22 g sugar, and 40 g protein. Sixty minutes into the training session subjects were provided with a commercially available electrolyte replacement beverage (Gatorade, Inc) containing 80 kcal, 21 g carbohydrates, and 21 g sugar. Upon training cessation participants were again provided food bars and shakes as well as a commercially available snack mix (Wal-Mart Stores, Inc.). The meal contained 600 kcal, 26 g fat, 52 g carbohydrate, 32 g sugar, and 44 g protein. At 2h post training participants consumed a standardized meal from a commercial location (Chipotle Mexican Grill) consisting of 1085 kcal, 33 g fat, 107 g carbohydrates, 3 g sugar, and 84 g protein. All participants were allowed water ad libitum. Total food intake for the data collection period was: 2225 kcal, 76 g fat, 218 g carbohydrates, 78 g sugar, and 168 g protein.

Exercise sessions

Subjects in the HI group participated in a single bout of training similar to what would be experienced in a military basic training environment. To achieve this effect the exercise session was led by senior members of the University of Kansas Army Reserve Officers' Training Corps (ROTC) staff. During the session lead instructors would alternate, allowing for the physical intensity to remain at a high level throughout the training program. All exercises had been pre-programmed prior to the session start with modification during the session to maintain intensity. Training consisted of a mix of aerobic activities (≤ 400 m), anaerobic body weight exercises, and anaerobic exercises utilizing 45 lbs weights with exercises quickly transitioning from one to the next to prevent recovery. The exercise bout lasted a total of 100 min. Scheduled 5 min rests were inserted at 30, 60, and 85 min after the initiation of the exercise session. During the scheduled rest periods, subjects were encouraged to consume water and a carbohydrate/electrolyte drink.

Subjects in the moderate-intensity group (MOD) participated in a 100 min bout of exercise training led by an exercise physiologist. Training consisted of similar activities as the HI group but performed at a pace allowing for in-session recovery. Scheduled 5 min rests were included at 30, 60, and 85 min after the initiation of the exercise session and MOD subjects were similarly encouraged to consume water and a carbohydrate/electrolyte drink.

Physiological monitoring

Participants were fitted with a Zephyr BioHarness 3 (Zephyr Technology, Annapolis, MD, USA) for HR measures. Continuous HR measures were recorded at 1 Hz intervals during the training session. HR data was downloaded using the Zephyr BioHarness Log Downloader (version 1.0.29.0). Five training zones were defined as follows: zone 1 <60% predicted maximum HR (HR_{max}); zone 2, 60%-70% HR_{max}; zone 3, 70%-80% HR_{max}; zone 4, 80%-90%;

and zone 5, >90% HR_{max}. HR_{max} was estimated using the methods of Tanaka et al. (167). HR, breathing rate and approximations of core temperature are logged by the Bioharness and interpreted using a proprietary Red/Orange/Green (ROG states) status indicator. Time in ROG states (Green: OK – vital signs within expected normal values. Orange: Alert – vital signs outside of "normal," observation recommended. Red: Alert – vital signs significantly outside of normal range) were recorded at 1 Hz intervals for analysis.

Blood collections

Blood draws were performed by physician-approved allied health care providers using standard phlebotomy techniques. Venous blood samples were obtained by venipuncture of the antecubital fossa at baseline, immediately post-training (Post), 1 h post-training, 4 h post, and 6 h post-training and placed in sodium EDTA, sodium heparin, serum separator tubes, and no anticoagulant Vacutainers as indicated.

Antibodies and reagents

Antibodies used for flow cytometry were: purchased from and include: anti-CD3-APC (BioLegend, San Diego, CA), and anti-CD152-PE (CTLA4 BioLegend, San Diego, CA). Cells were stained with 2.0 μM 5-(and-6)-carboxyfluorescein diacetate, succinimidyl ester (CFSE, BioLegend, San Diego, CA) on day 0 of stimulation for proliferation assays. Flow cytometry was performed using an Accuri C6 (BD Accuri Cytometers, Ann Arbor, MI) and data analysis using CFlow Plus (Accuri).

Measurement of catecholamines, cortisol and complete blood counts

Peripheral blood was collected in a serum separator tube (8 ml) for analyses of cortisol. Blood (6 ml) was collected in vials containing EDTA for analyses of complete blood counts (CBC) and catecholamines. Cortisol concentrations and CBC were assessed commercially by immunoassay and cytometry methods (Quest Diagnostics Laboratories, Lenexa, KS). Plasma for catecholamine (epinephrine and norepinephrine) analyses was obtained by centrifugation at 2000 *g* for 10 min at 4˚ C and stored at -80˚C until analysis. Catecholamine concentrations were determined using BI-CAT ELISA kits according to the manufacturer's instructions (Eagle Biosciences, Inc, Nashua, NH) using a Synergy microplate reader (BioTek, Winooski, VT, USA).

Cell purification and culture

Peripheral blood (10 ml into sodium heparin) was obtained at each time point for analyses of T cell proliferation. Peripheral blood mononuclear cells (PBMC) were isolated using Ficoll-Paque PLUS (GE Healthcare, Piscataway, NJ) density gradient centrifugation. Total T cells were purified from washed PBMC by E-rosetting. Briefly, PBMC were incubated with AET-treated sheep red blood cells (RBC, Hemostat Laboratories) for 10 min at 37˚ C. Cells were pelleted and held on ice for 30 min, re-suspended in the same fluid, and centrifuged over a Ficoll-Paque PLUS density gradient. T cells from the pellet were cleared of red blood cells by lysis in ACT (17 mM Tris, 0.83% NH4Cl, pH 7.2), and washed three times. Cells were cultured immediately at 37˚ C with 5% CO2 in complete RPMI 1640 (Mediatech, Herndon, VA) containing 10% fetal bovine serum (Atlanta Biologicals, Lawrenceville, GA), 50 U/ml each of penicillin and streptomycin (Life Technologies, Grand Island, NY), and 20 mM L-glutamine (Life Technologies).

T cell stimulation

T cell proliferation was analyzed in response to co-stimulation through CD3+CD28 using either plate-bound antibodies, phytohaemagglutinin (PHA) treatment, or no simulation. Each antibody was titrated to the lowest concentration that gave maximum T cell proliferation: anti-CD3 (OKT3) used at 1 μg/ml (BioLegend, San Diego, CA) and anti-CD28 (CD28.2) at 2 μg/ml (BioLegend, San Diego, CA). Antibodies were diluted to indicated concentration in sterile Dulbecco's PBS (Life Technologies) and incubated in 96 well plate overnight at 4˚C; unbound Antibodies were removed by washing 3X with dPBS immediately before cell plating. Total T cells were plated at 1.5 x 10^6 cells/ml in 200μl complete RPMI 1640 directly after isolation. Stock 5 mg/ml PHA (Sigma-Aldrich, St. Louis, MO) was diluted into complete medium before use and added to appropriate wells immediately following cell plating to final concentration of 2.5 ug/mL. . Cells were incubated for 6 d at 37˚ C in a humidified incubator with 5% CO_2 and then analyzed by flow cytometry

Serum cytokines, creatine kinase, and high mobility group box 1 protein

Peripheral blood (8ml) was collected into at tube containing no anticoagulant. Serum for analyses was obtained after clotting by centrifugation at 2000*g* for 10 min at 4˚ C and stored at -80˚ C until analysis. Peripheral concentrations of IFN-γ, IL-10, IL-17a, IL-1β, IL-2, IL-4, IL-5, IL-6, and TNF-α were determined using a human cytokine magnetic bead panel kit (HCYTOMAG-60K-13) (Millipore, Billerica, MA, USA). The samples were detected and analyzed using a Luminex 200 System (Luminex Corp, Austin, TX). Creatine kinase (CK) enzyme concentrations were computed using a CK reagent kit (Pointe Scientific, Inc. Canton,

MI). The samples were measured using a Synergy microplate reader (BioTek, Winooski, VT) at 340 nm at 1, 2 and 3 minutes. HMGB1 concentrations were measured using Human HMGB1 Elisa kits (NeoBioLab, Cambridge, MA). The results were read at 450 nm using a Synergy microplate reader (BioTek, Winooski, VT, USA). All ELISA procedures were performed according to the manufacturer's instruction.

Statistical analysis

Data were analyzed using two-way mixed factorial ANOVA (group [HI x MOD] x time [1 vs. 2 vs. 3 … vs. 5]). When appropriate, follow-up analyses were performed using independent samples t-tests and ANOVA models with Bonferroni corrections. The level of significance was set at $\alpha = 0.05$. All statistical analyses were performed using SPSS 22 (IBM Corporation, Armonk, New York, USA).

3.3 Study 3: Immunoendocrine responses to the Marine Corps Martial Arts Program

Subjects

Thirty-six male, active duty, newly enlisted U.S. Marines were recruited for this investigation (age = 19 ± 1 yrs; height = 175 ± 7 cm; weight = 74 ± 7 kg). Six cohorts were recruited over a period of 18 months with each cohort being observed 3 times with 3 weeks between each visit. All Marines had recently graduated Recruit Training and the School of Infantry and were reporting to the Marine Corps detachment based in Fort Leonard Wood, MO for formal training in their assigned Military Operational Skill (MOS). Subjects provided informed consent and completed a medical history questionnaire prior to participation. At the time of recruitment, subjects were instructed to maintain their normal physical activity and

dietary patterns leading up to data collection. This implied that subjects would be in a non-fasted state at the time of data collection. This study was approved by the University Institutional Review Board for Human Subjects at the University of Kansas, Lawrence and the U.S. Marine Corps Human Research Protection Program in Washington D.C.

Training Session

The Marines arrived at the testing location at 0530 hours for baseline assessment and began the training session at 0600 hours. MCMAP training consists of approximately 30 min of Combative Conditioning (CC) involving a variety of exercises including but not limited to sprints, calisthenics and partner carries/drags. The CC component is followed by approximately 30 min of Combative Arts (CA) under the supervision of a MCMAP instructor. The CA portion involves skill instruction and practice at varying intensities. In addition to the physical stress of training, the Marine's performance is constantly being evaluated/corrected by the MCMAP instructor.

Physiological monitoring

Participants were fitted with a Zephyr BioHarness 3 (Zephyr Technology, Annapolis, MD, USA) for heart rate (HR) measures. Continuous HR measures were recorded at 1Hz intervals during the training session. HR data were downloaded using the Zephyr BioHarness Log Downloader (version 1.0.29.0). Five training zones were defined as follows: zone 1 <60% predicted maximum HR (HR_{max}); zone 2, 60%-70% HR_{max}; zone 3, 70%-80% HR_{max}; zone 4, 80%-90%; and zone 5, >90% HR_{max}. HR_{max} was estimated using the methods of Tanaka et al. (167).

Blood collections and analyses

Blood draws were performed by physician-approved allied health care provider using standard phlebotomy techniques. Venous blood samples were obtained by venipuncture of the antecubital fossa at baseline. Following the training session, an intravenous catheter (Braun, 18 g, 32 mm) was inserted into the antecubital vein, and a small bore extension set (Braun, 20 cm) was attached. Venous blood samples were collected immediately after training end (IP) and every 15 min for 1 h post-training (R15, R30, R45, and R60) in sodium EDTA, sodium heparin, serum separator tubes, and no anticoagulant Vacutainers as indicated. For each post-training blood collection, approximately 1 ml of blood (with saline from the extension set) was drawn into a discard tube prior to the sample draw.

NE, EPI, CORT, immunoglobulin (Ig)-G, IgM, complete blood count (CBC), neutrophil oxidative burst and lymphocyte subsets were determined from blood samples obtained immediately after training end (IP) and every 15 min for 1 h post-training (R15, R30, R45, and R60). Peripheral blood was collected in a serum separator tube (16 ml) for analyses of cortisol and immunoglobulins. Blood (6 ml) was collected in vials containing EDTA for analyses of complete blood counts (CBC) and lymphocyte subsets. Peripheral blood (16 ml into sodium heparin) was obtained for analyses of catecholamines and neutrophil oxidative burst function. Cortisol levels, IgG, IgM, and CBC were assessed commercially by immunoassay, immunoturbidimetric, and cytometry methods respectively (Quest Diagnostics Laboratories, Lenexa, KS). Catecholamines (EPI and NE) were assessed commercially by high performance liquid chromatography (HPLC) with electrochemical detection (Quest Diagnostics Laboratories, Chantilly, VA). Lymphocyte subsets including absolute and percent CD3, CD4, CD8, CD19,

CD16/56 and total lymphocytes and neutrophil oxidative burst function were assessed commercially by flow cytometry (Quest Diagnostics Laboratories, St. Louis, MO; Quest Diagnostics Laboratories, San Juan Capistrano, CA).

Statistical analysis

The data were naturally arranged in a hierarchical structure (i.e. time nested within visits, nested within subjects). We performed three-level multilevel models with the repeated measures for time as the level 1 measurement, visit as the level 2, and subject as level 3. The main analysis focused on change over time for each parameter after controlling for baseline concentrations. Preliminary analyses found 1.4% missing data in our data set. Given the localization of the missing data and our knowledge of why it occurred, these data points were classified as missing completely at random and imputed (168). Missing data imputation was performed using the *mice* (169) package and the *lme4* package in R version 3.0.1 (170) was used for model analyses. Random intercepts and slopes were specified for subjects as well as for time. Fixed effects for time (linear, quadratic, and cubic) were tested using nested model tests. Overall, significant predictors at $p < 0.05$ were retained. Ancillary analyses employed procedures for analyzing serial measurements (171). Specifically, variables were quantified using area-under-the-curve (AUC) and peak value. Serial measures were subsequently analyzed using repeated measures ANOVAs.

Chapter 4: Results

4.1 Study 1: T Cell Proliferation and Activation Following Exercise

4.1.1 Acute exercise induced substantial changes in heart rate and ratings of perceived exertion

The acute exercise trial elicited a substantial sympathetic stimulus as demonstrated by the summative time spent in heart rate zones. The mean predicted HR_{max} for all subjects was 190 ± 3 bpm. Average HR during the EX trial was 150 ± 15 bpm compared to an average of 79 ± 7 bpm in the CT session. Summative time in HR zones for the EX trial were: zone 1: 4.6 ± 4.4 min; zone 2: 3.5 ± 2 min; zone 3: 7.8 ± 4.1 min; zone 4: 6.4 ± 3.6 min; and zone 5: 9.2 ± 6.7 min. Average RPE during the EX trial was 14. The entirety of the 30 min CT session was spent under the zone 1 threshold with an average RPE of 6.

4.1.2 T cell proliferation responses to PHA increased post exercise

Acute exercise significantly increased T cell proliferation relative to the control trial with a significant trial x time interaction effect observed for both the percent of proliferating cells ($p=0.026$) and total number of divided cells ($p=0.048$) (Fig. 1). There were no significant changes in PHA stimulated proliferation measures pre-to-post CT session. It did not appear that T cell proliferation via PHA was adversely impacted when cells were rested in whole blood overnight suggesting it would be a fairly robust stimulant for delayed isolation protocols (Fig. 2). There were no significant differences in pre-trial PHA stimulated proliferation measures for the EX and CT conditions.

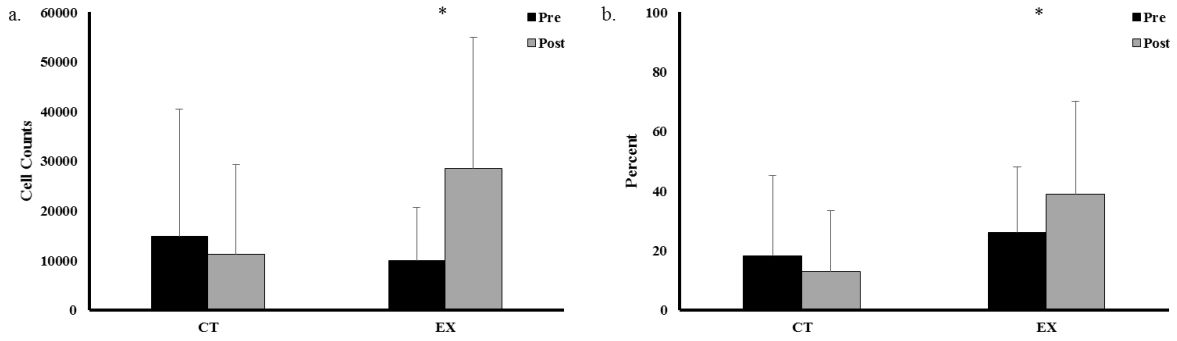

Fig. 1. PHA stimulated cell counts increased following the exercise condition. a) PHA stimulated cell count data. b) PHA stimulated percent data. All values have been normalized to baseline. Values are presented as means ± SD. * indicates significant difference from Pre.

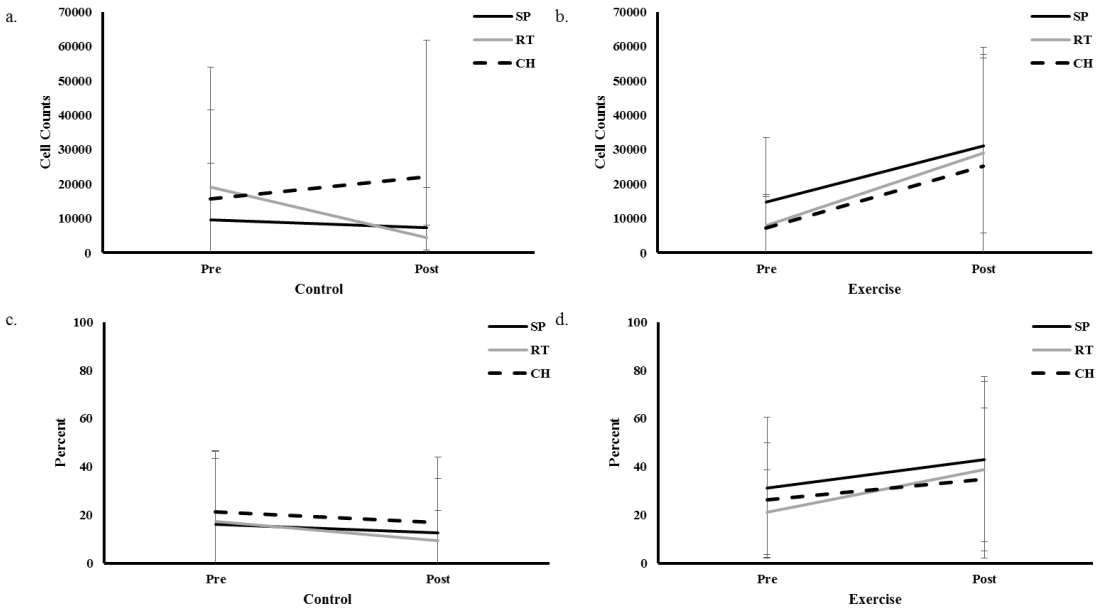

Fig. 2. PHA stimulated T cell proliferation measures are relatively stable across delayed isolation protocols. a) Control trial cell count measures. b) Exercise trial cell count measures. c) Control trial percent of cells dividing. d) Exercise trial percent of cells dividing. Values are presented as means ± SD. SP: Standard Protocol; RT: Overnight at Room Temperature; CH: Overnight at 4˚C.

4.1.3 CD3+CD28 proliferation affected by isolation protocol

Exercise-induced T cell proliferation increased when cells were stimulated with CD3+CD28, but there were no significant trial x time interactions for either percent changes in proliferation (p=0.094) or cell count data (p=0.902). T cell delay protocols did significantly

impact both measures, however, with trial x delay interaction effects observed for both percent (p=0.019) and count data (p=0.042). Follow up analyses uncovered no significant differences among delay conditions for the CT session, but did reveal significant differences in the EX trial.

The SP method had significantly higher proliferation values for both percent and cell counts when compared to the RT (percent: p=0.048; count: p=0.036) and CH (percent: p=0.026; count: p=0.085) delayed isolation protocols (Fig. 3). Proliferation increased following exercise relative to the control session using the SP method but failed to reach statistical significance for either percent (p=0.078) or count data (p=0.051). The lack of significance is likely a result of small sample size and future work will need to address whether this finding holds in larger studies.

Allowing cells to rest overnight in whole blood, whether at room temperature or 4˚ C, lessened the exercise-induced stimulus for proliferation rendering both the RT and CH samples closer to the CT trial (Fig. 4).

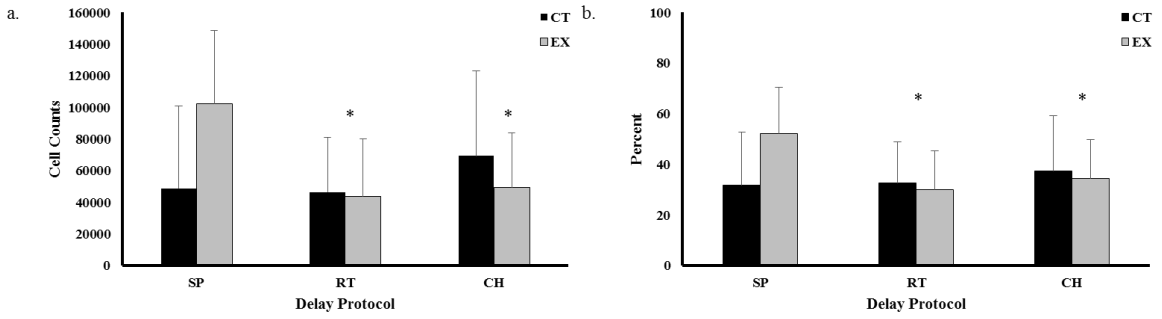

Fig. 3. Proliferation measures for CD3+CD28 stimulated T cells were depressed when cells were rested overnight in whole blood. a) Cell count data. b) Percent data. Values are presented as means ± SD. SP: Standard Protocol; RT: Overnight at Room Temperature; CH: Overnight at 4˚C. * indicates statistically significant difference from SP.

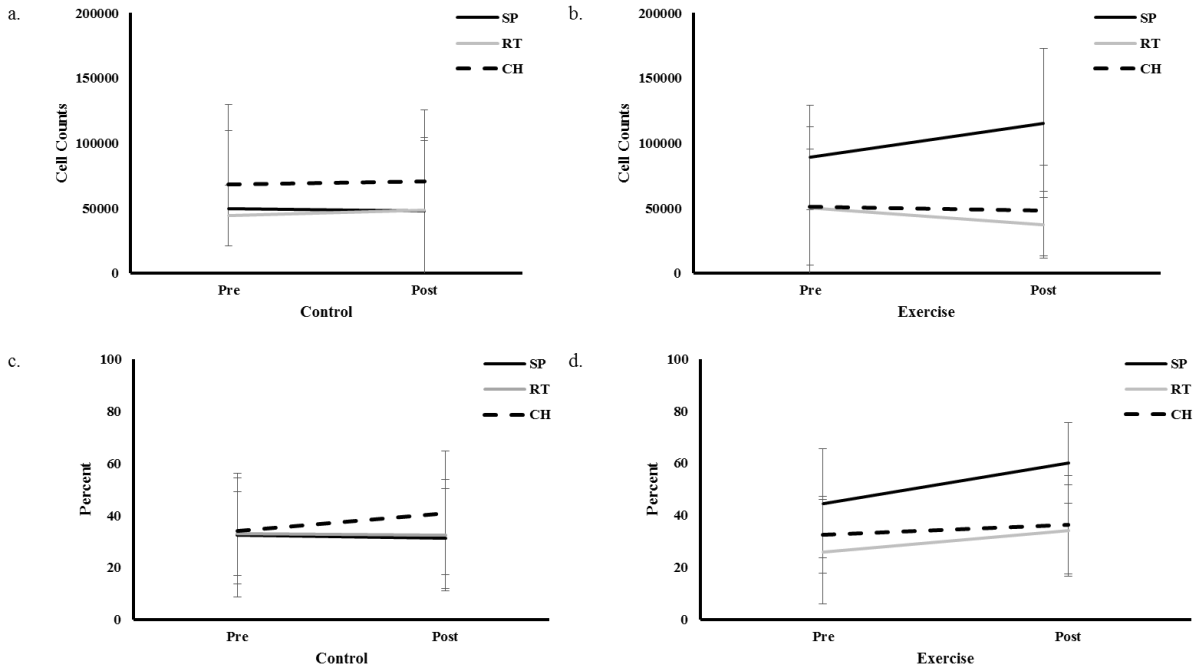

Fig. 4. Measures CD3+CD28 stimulated T cell proliferation post-exercise are negatively impacted by delayed cell isolation. a) Control trial cell count measures. b) Exercise trial cell count measures. c) Control trial percent of cells dividing. d) Exercise trial percent of cells dividing. Values are presented as means ± SD. SP: Standard Protocol; RT: Overnight at Room Temperature; CH: Overnight at 4˚C.

4.1.4 Activation of PHA stimulated T cells marginally increased with exercise

Although the level of PHA induced proliferation increased significantly from pre-to-post exercise, the trial x time interaction effect did not remain significant when looking at $CD4^{-}CD25^{+}$ ($p=0.078$) and $CD4^{+}CD25^{+}$ ($p=0.057$) cell counts (Fig. 5). There were no significant differences uncovered for percent changes in either of these cell populations.

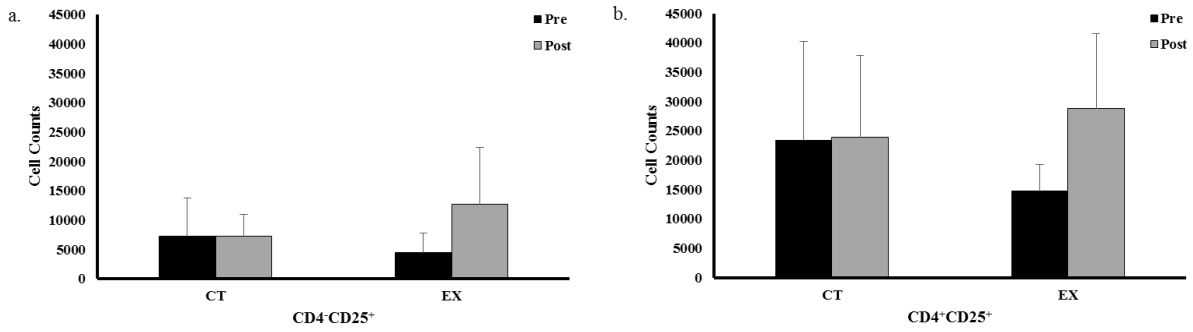

Fig. 5. PHA stimulated cell activation in $CD4^-$ and $CD4^+$ cells marginally increased post-exercise. a) PHA stimulated cell count data for $CD4^-CD25^+$ T cells. b) PHA stimulated cell count data for $CD4^+CD25^+$ T cells. Values are presented as means ± SD.

There was a significant time x delay interaction for $CD4^-CD25^+$ cells (p=0.014). Follow-up analyses indicated that while there were no differences within trial sessions, the SP and CH isolations both saw substantial increases in activated cell counts from pre-to-post (SP: p=0.076; CH: p=0.012). The RT isolation also had higher values for the post measure but did not reach a significant level (p=0.338). Figure 6 represents cell activation responses pre-to-post trial and by isolation protocol.

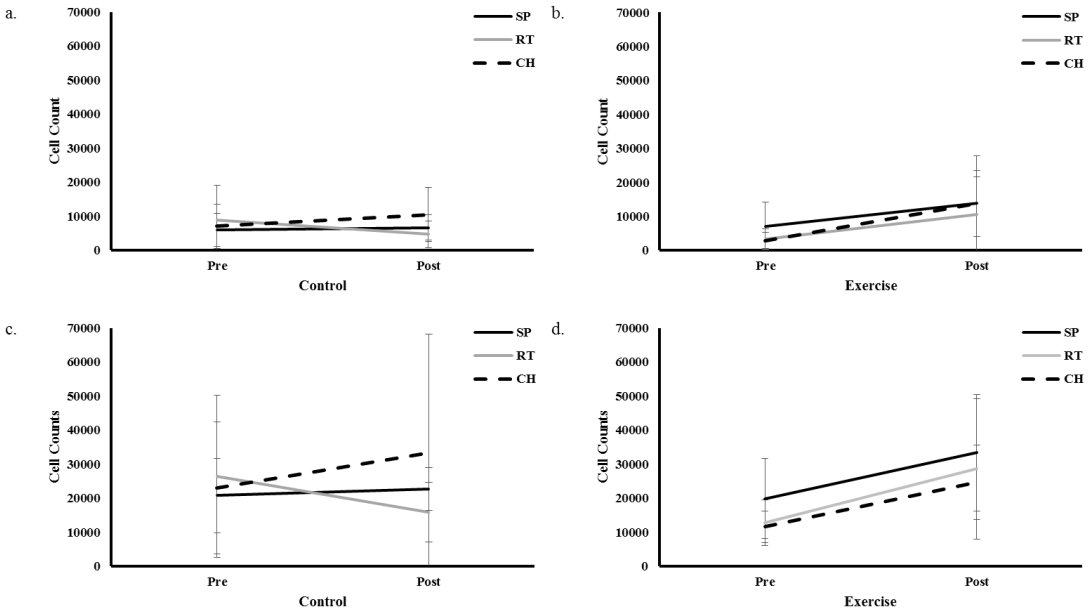

Fig. 6. PHA stimulated T cell activation post-exercise is minimally impacted by cell isolation delays. a) Control trial $CD4^{-}CD25^{+}$ cell count measures. b) Exercise trial $CD4^{-}CD25^{+}$ cell count measures. c) Control trial $CD4^{+}CD25^{+}$ cell count measures. d) Exercise trial $CD4^{+}CD25^{+}$ cell count measures. Values are presented as means ± SD. SP: Standard Protocol; RT: Overnight at Room Temperature; CH: Overnight at 4˚C. * indicates statistically significant difference from SP.

4.1.5 Delay protocol affects markers of CD3+CD28 stimulated T cell activation

T cell activation following stimulation with CD3+CD28 was again disproportionately influenced by the delay protocol used for T cell isolation from whole blood. $CD4^{-}CD25^{+}$ cells had a significant trial x delay interaction for cell counts (p=0.019) as well as percent of cells activated (p=0.028). Examination of cell count data (Fig. 7a) found significantly elevated levels of $CD25^{+}$ cells following the SP isolation relative to RT (p=0.038) and CH (p=0.029). Further, the EX trial exhibited a significantly greater number of activated cells relative to the CT trial when using the SP isolation (p=0.04). The percent of activated $CD4^{-}$ cells paralleled this result with SP showing increased values compared to RT (p=0.032) and CH (p=0.066). The increased values in the EX trial did not reach a significant level compared to CT (p=0.069).

$CD4^+CD25^+$ cell counts post-exercise did not exhibited significant decreases (p=0.087) in activation after resting overnight (Fig. 7b). There was a main effect for delay (p=0.026) with SP increased relative to both RT and CH isolations. Figure 8 represents cell activation responses pre-to-post trial and by isolation protocol.

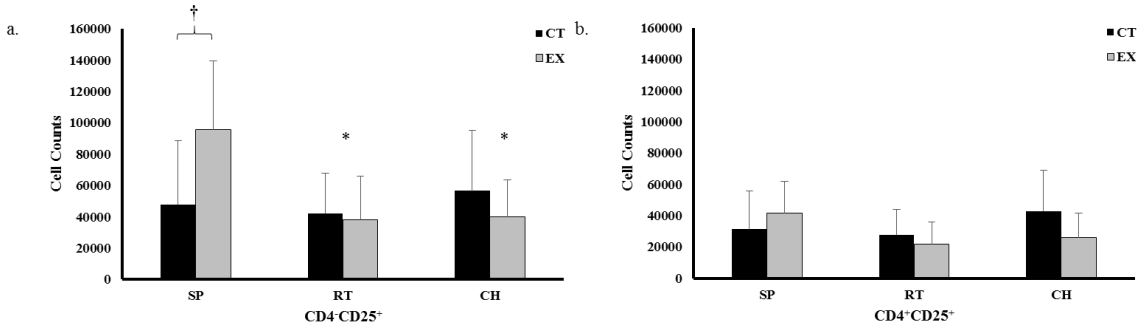

Fig. 7. Post-exercise T cell activation following CD3+CD28 stimulation exhibits a greater increase $CD4^-$ cell populations. a) $CD4^-CD25^+$ cell counts. b) $CD4^+CD25^+$ cell counts. Values are presented as means ± SD. † indicated a significant difference between trials. * indicates a significant difference from SP.

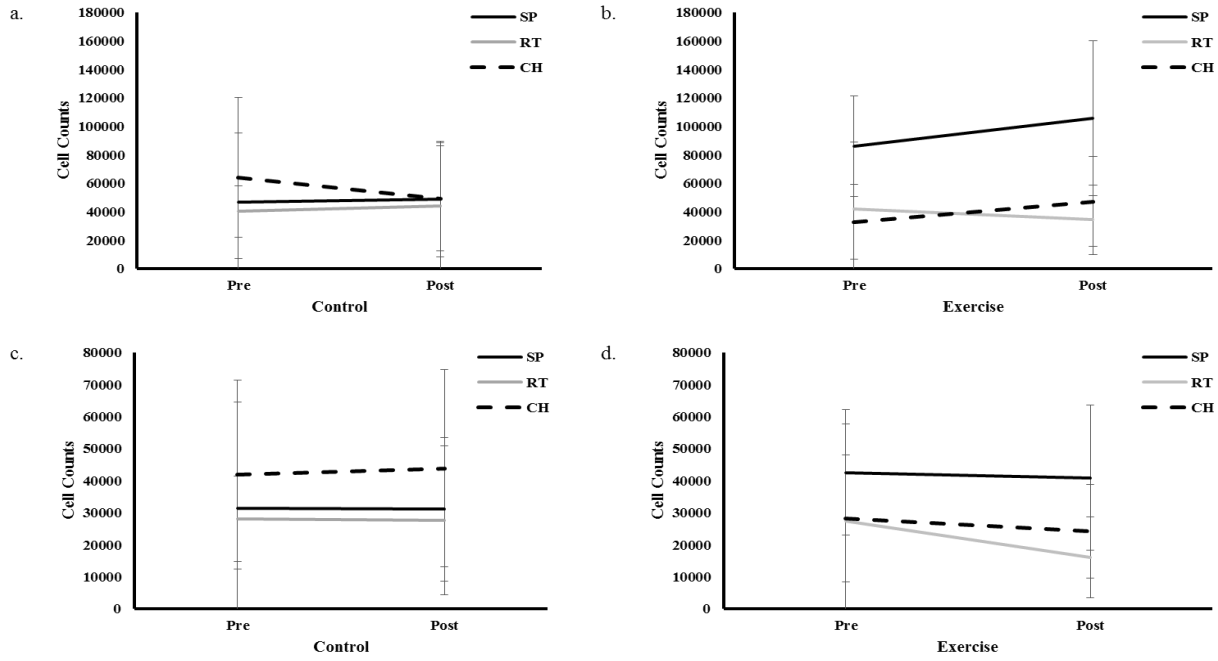

Fig. 8. Exercise-induced measures of CD3+CD28 stimulated T cell activation are decreased following overnight delays in T cell isolation. a) Control trial $CD4^-CD25^+$ cell count measures. b) Exercise trial $CD4^-CD25^+$ cell count measures. c) Control trial $CD4^+CD25^+$ cell count measures. d) Exercise trial $CD4^+CD25^+$ cell count measures. Values are presented as means ± SD. SP: Standard Protocol; RT: Overnight at Room

4.2 Study 2: Do Military and Tactical Experiences Model the Characteristic Exercise Response

4.2.1 Heart rate and approximate core temperature differed significantly by group

Average HR during the training session was significantly elevated in HI compared to MOD groups (158 ± 6 bpm vs. 130 ± 9 bpm; $p<0.001$) with a significant group x time interaction effect ($p<0.001$) for time in heart rate zones (Fig. 1). Time spent in each respective heart rate zone significantly differed between groups. Significant differences between approximate measures of mean ($p<0.001$) and peak ($p=0.002$) core body temperature were also observed between HI and MOD groups during the training sessions (mean: 38.6 ± 0.3 vs. 37.9 ± 0.2; peak: 39.3 ± 0.5 vs. 38.4 ± 0.4 respectively) although these are not likely to be biologically relevant in this context. Further, a significant group x time interaction was identified for percent of time spent in the individual ROG states ($p<0.001$). Together these data suggest the HI group testing session engendered a significantly greater physiological stress response relative to the MOD session.

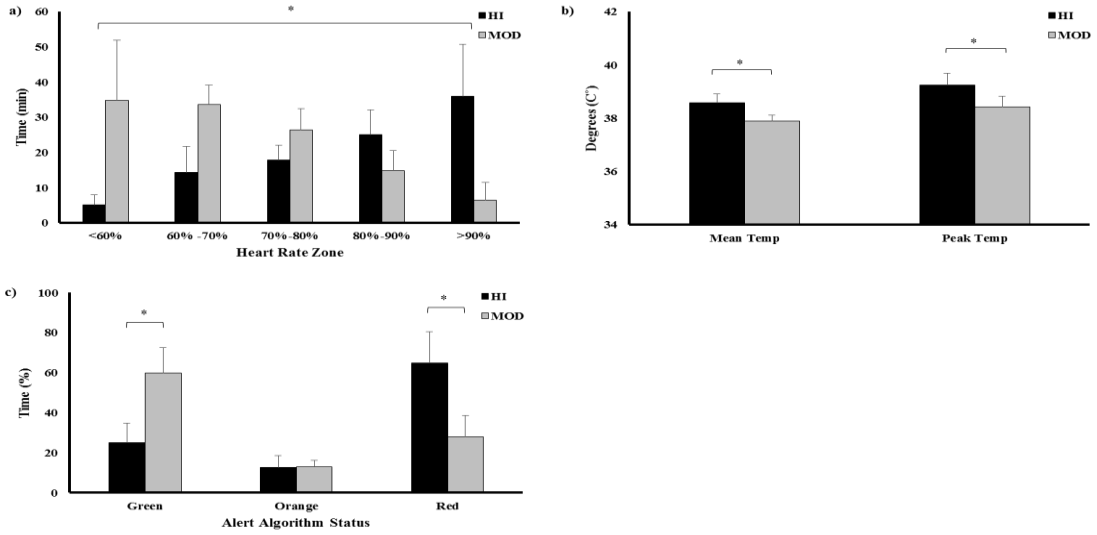

Fig. 1. Measures of training intensity significantly differed by group. a) Time spent in heart rate zones during training session, b) Approximate measures of core body temperature during training, and c) Time in Bioharness Alert Algorithm Status (ROG states). Green: OK – vital signs within expected normal values. Orange: Alert – vital signs outside of "normal," observation recommended. Red: Alert – vital signs significantly outside of normal range, action may be needed. Values are presented as means ± SD. * Indicates significantly different between groups.

4.2.2 Endocrine responses marginally elevated in high intensity session

Analyses of catecholamine measures did not uncover any significant group x time interaction effects (Fig. 2). Both EPI ($p<0.001$) and NE ($p=0.003$) did, however, exhibit main effects for time. There was a significant group x time interaction for CORT ($p=0.028$) with a significantly higher concentration observed in the HI compared to MOD group at the Post measure ($p=0.011$). There were no significant differences in baseline endocrine concentrations between groups.

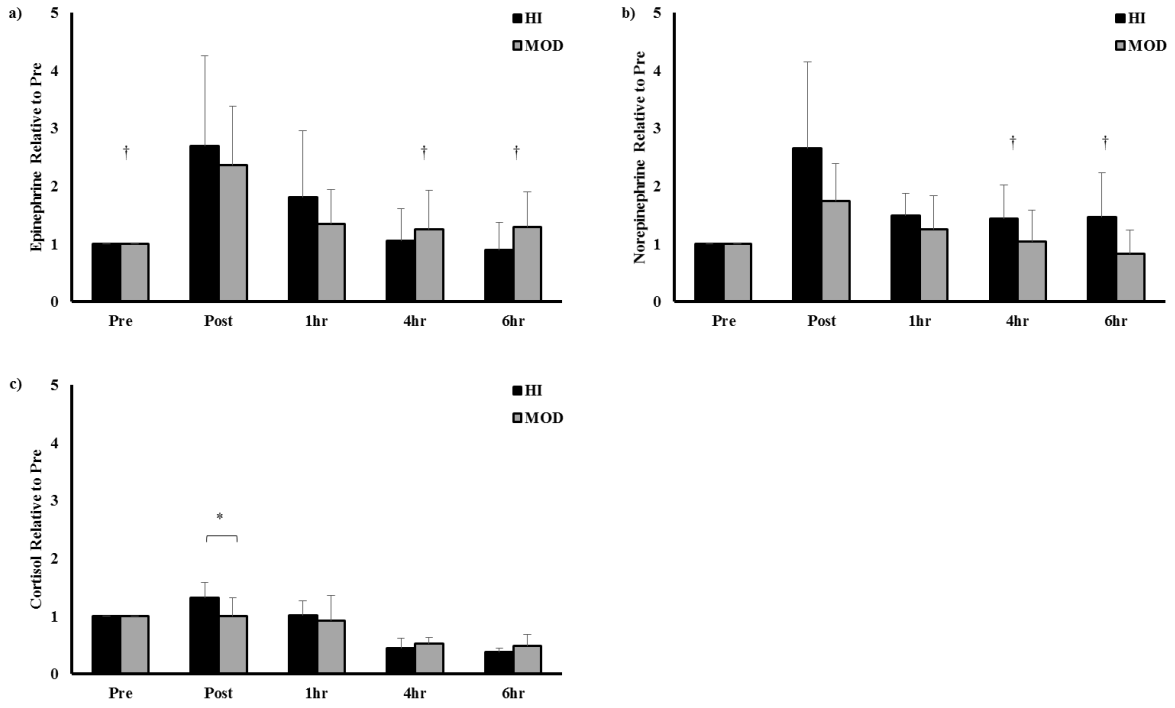

Fig. 2. Endocrine concentrations relative to Pre measures increased following training sessions. a) Epinephrine, b) Norepinephrine, and c) Cortisol. All values have been normalized to Pre. * Indicates significantly different between groups. † indicates significantly different from Post.

4.2.3 T cell proliferation significantly increased in the high intensity group

Phytohaemagglutinin stimulated T cell proliferation cell counts ($p=0.025$) and percent ($p<0.01$) were significantly increased in the HI group at all time points, including the baseline measures, relative to the MOD. Due to the significant difference in baseline measures, we examined the curve profiles of proliferation responses following each session. Figure 3 shows proliferation response curves normalized to baseline for cell count data. While the MOD groups say no significant changes over time, the HI group saw an immediate, and significant ($p=0.021$), increase in cell proliferation at the Post measure.

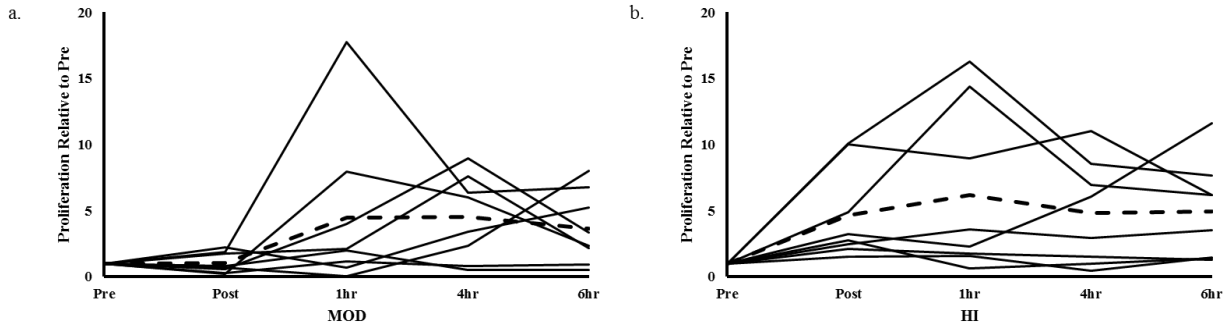

Fig. 3. PHA stimulated T cell proliferation increased immediately in the HI group compared to MOD. a) Moderate Intensity group cell count data. b) High Intensity group cell count data. All values are normalized to the Pre time point. - - - Indicates mean response curve.

A similar group x time interaction effect was observed for counts ($p<0.001$) and percent ($p<0.001$) of T cells stimulated using CD3+CD28 (Fig. 4). Only the HI group was significantly increased at the Post measure ($p<0.001$) while both groups were significantly elevated at 4 h and 6 h relative to their baseline controls. We did identify significant differences between groups (Fig. 5) at the Pre ($p=0.02$), Post ($p<0.001$), and 1 h ($p=0.003$) measures where it was evident that the HI group responded to the training session with enhanced proliferation whereas the MOD group's proliferative capacity was classically suppressed following training.

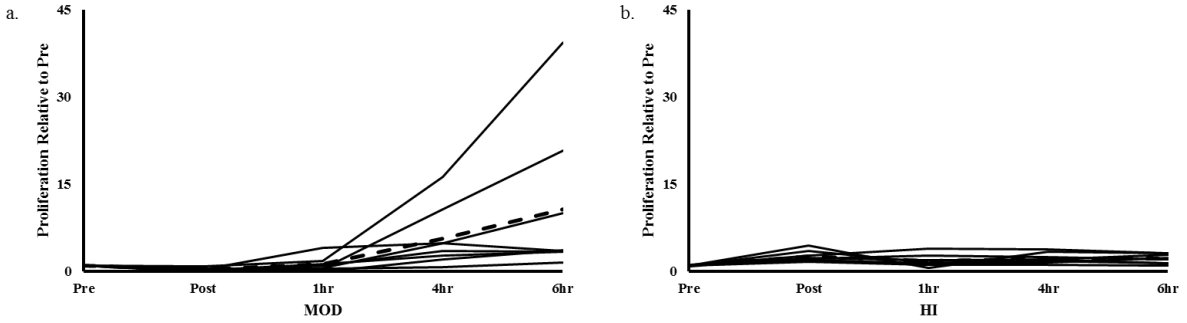

Fig. 4. CD3+CD28 stimulated T cell proliferation increased immediately in the HI group compared to MOD. a) Moderate Intensity group cell count data. b) High Intensity group cell count data. All values are normalized to the Pre time point. - - - Indicates mean response curve.

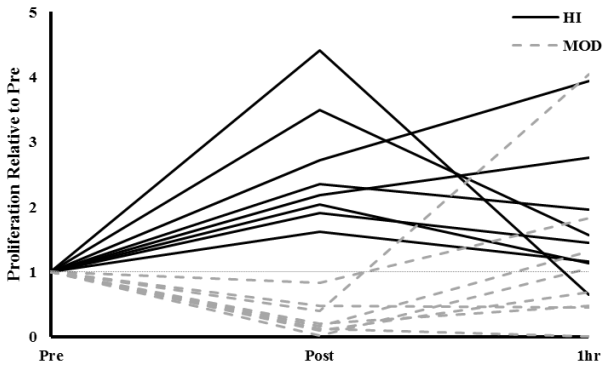

Fig. 5. HI group participants showed a tendency toward increased proliferation post-session while the MOD group's proliferation was suppressed at the same time point.

4.2.4 Alterations in peripheral cytokine concentrations do not explain changes in cell proliferation

Given the variation in proliferative responses we expected to see cytokine profiles indicative of increased T cell activity. To the contrary, we found that cytokine measures for a number of immunomodulatory cytokines were below detectable limits for the majority of our samples. These cytokines included: IL-1β, IL-2, IL-4, IL-5, and IL-6.

A significant group x time interaction effect ($p=0.004$) was observed for IL-10 with the HI group have significantly higher concentrations at Post ($p=0.013$). Peripheral concentrations remained elevated in this group at 1 h but did not maintain a level of statistical significance ($p=0.055$) (Fig. 6). While the MOD group saw little to no change across time measures, the HI group exhibited not only similarly scaled increases but also shared the same kinetic profile post-training suggestive of a strong patterned response to the training session.

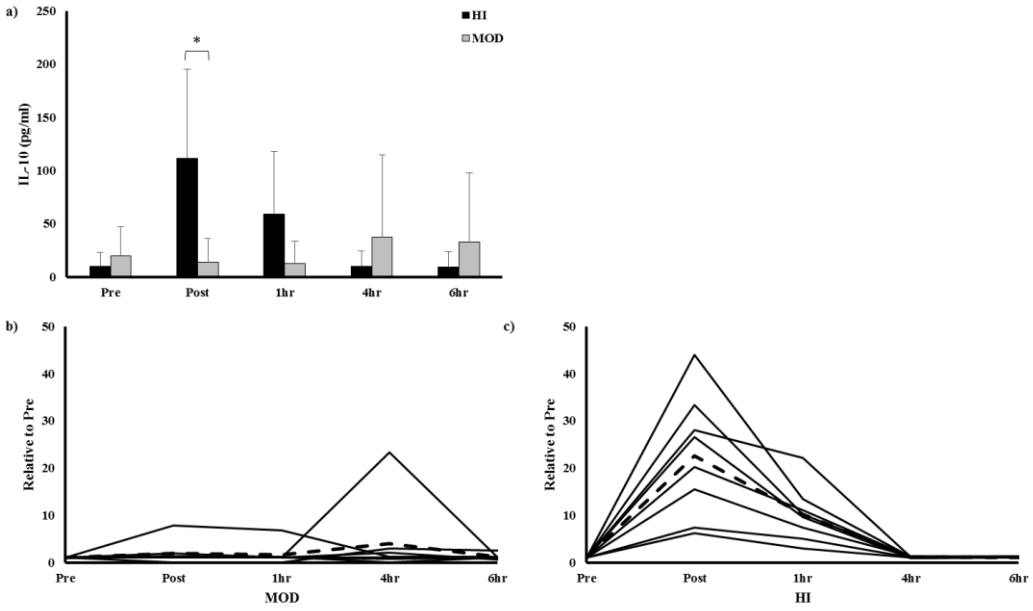

Fig. 6. IL-10 responses significantly elevated in HI group post training. a) IL-10 responses between groups following the two training sessions differed at the Post measure (Mean ± SD), b) Individual response curves for MOD participants normalized to Pre concentrations, and c) Individual response curves for HI participants normalized to Pre concentrations. * Indicates significantly different between groups. - - - Indicates mean

TNF-α exhibited a similar group x time interaction effect (p=0.012) (Fig. 7) with the HI group having elevated concentrations at both the Post (p=0.023) and 1 h (p=0.038) measures relative to the MOD session. The observed concentrations were not as large as those observed for IL-10, but represent a similar profile in terms of the response curve over the recovery period. Expecting that the TNF-α concentrations may have been muscle-derived, CK was also investigated but no significant differences were observed between groups (Fig. 8).

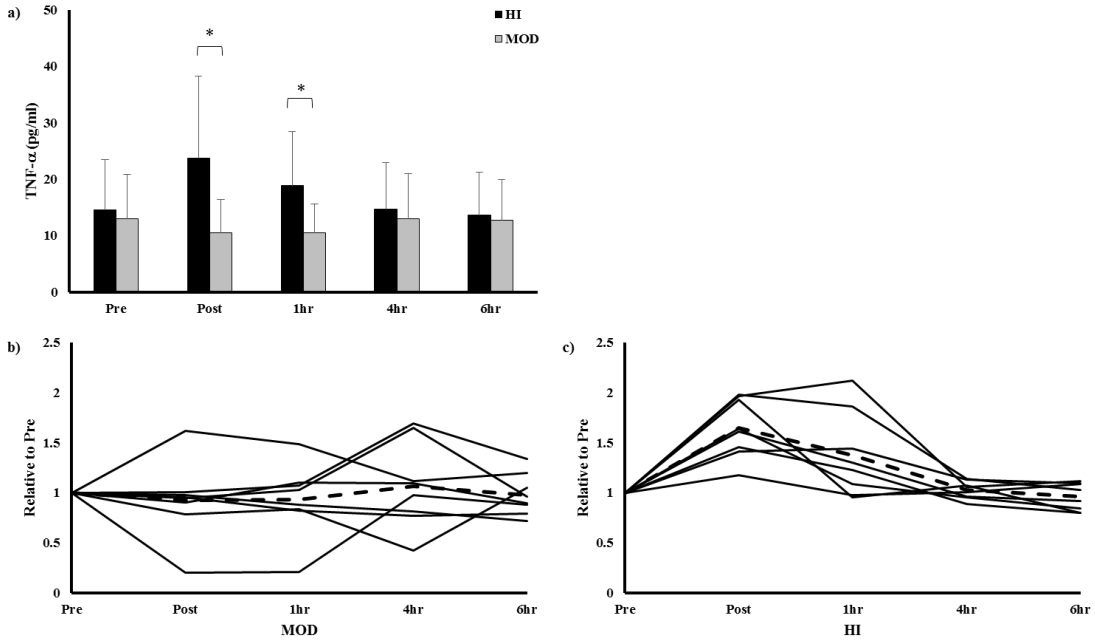

Fig. 7. TNF-α responses significantly elevated in HI group post training and out to 1 hr. a) TNF-α responses between groups following the two training sessions differed at the Post and 1 hr measures (Mean ± SD), b) Individual response curves for MOD participants normalized to Pre concentrations, and c) Individual response curves for HI participants normalized to Pre concentrations. * Indicates significantly different between groups. - - - Indicates mean response curve.

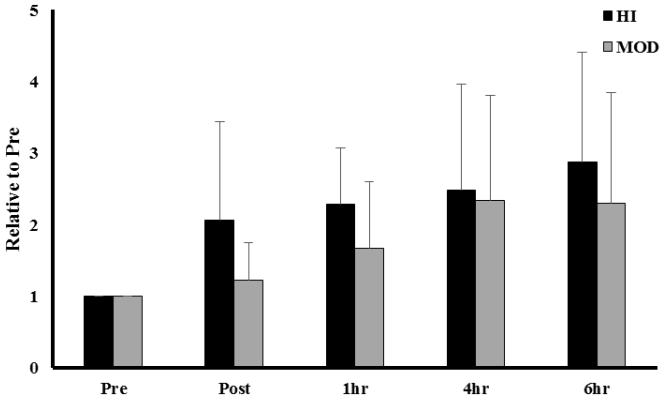

Fig. 8. Creatine kinase concentrations tended to increase over the recovery period with no significant interaction effects identified. Values are normalized to Pre concentrations.

4.2.5 CTLA-4 and HMGB1 concentrations not responsible for changes in functional immune responses

There was a significant group x time interaction effect (p=0.017) for mean fluorescence intensities (MFI) of CTLA-4 in cells stimulated with CD3+CD28. The HI group had significantly elevated values at the Post measure (p=0.031) with no other time points being significantly different (Fig. 9). The MOD group, however, saw an increase at the 4 h time point relative to the HI group, but it was not statistically significant (p=0.096). There were no significant interaction effects for PHA stimulated cells.

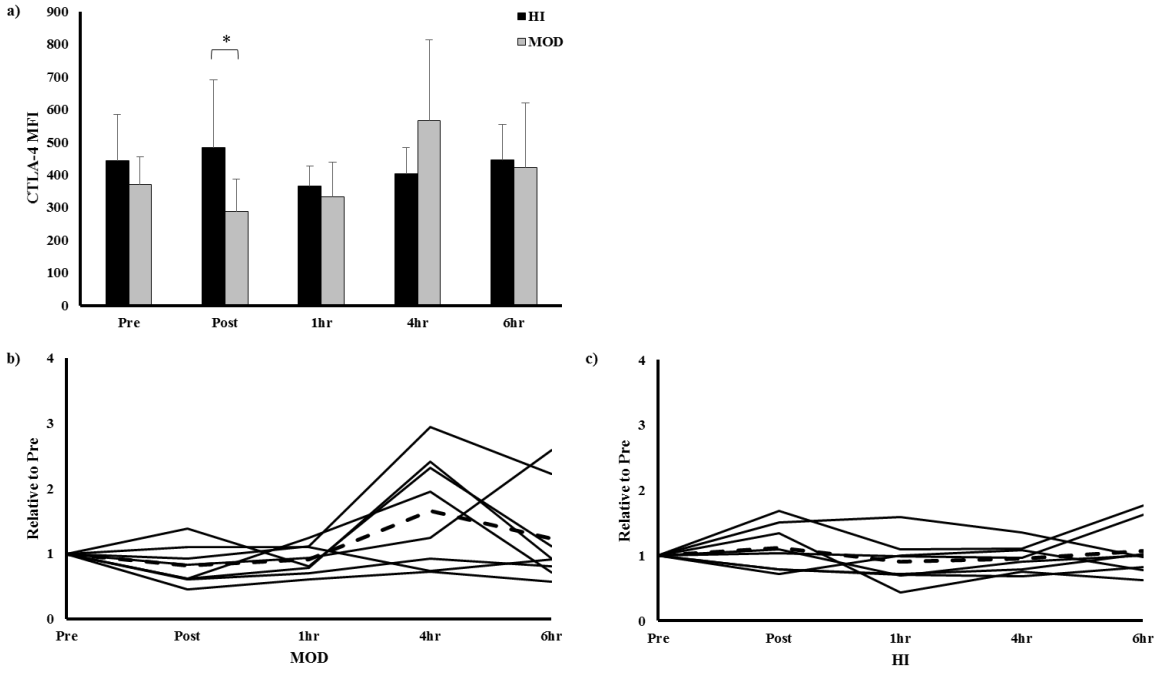

Fig. 9. Mean fluorescence intensity of CTLA-4 following CD3+28 stimulation elevated in HI group post-training. a) CTLA-4 MFI between groups following the two training sessions differed at the Post measure (Mean ± SD), b) Individual response curves for MOD participants normalized to Pre measures, and c) Individual response curves for HI participants normalized to Pre measures. * Indicates significantly different between groups. - - - Indicates mean response curve.

High mobility group box-1 protein (HMGB1), a marker of oxidative stress, was also investigated as a potential mechanism for increased T cell proliferation. There were no significant interaction effects observed over the time points measured. There was, however, some variability in individual response curves between groups suggestive of possible training derived alterations but no statistically significant changes were observed (Fig. 10).

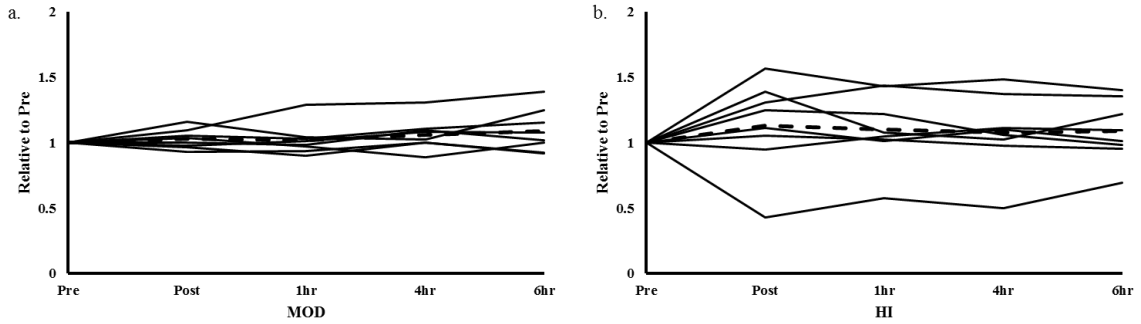

Fig. 10. Individual response curves for peripheral HMGB1 concentrations. a) MOD, b) HI. Values have been normalized to Pre. - - - Indicates mean response curve.

4.2.6 Leukocyte responses to training did not significantly differ by group

All immune parameters exhibited significant main effects for time but only neutrophil cell counts displayed a significant group x time interaction effect (p=0.004) (Fig. 11). The HI group had significantly elevated neutrophil counts at the Post (p=0.045) and 1 hr (p=0.027) time points. All other leukocyte measures demonstrated characteristic cell trafficking alterations with both cell counts and percentages decreased immediately post training and rising to, or above, baseline values during the recovery period.

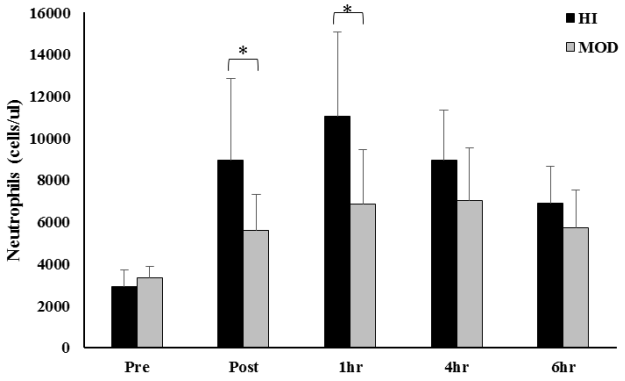

Fig. 11. Neutrophils significantly elevated in the HI group. Values are presented as means ± SD. ***** Indicates significant difference between groups.

4.3 Study 3: Immunoendocrine responses to the Marine Corps Martial Arts Program

4.3.1 Heart rate response to training

The MCMAP is an effective exercise stimulus as demonstrated by the summative time in heart rate zone data (Fig. 1), with approximately 27 min of each visit spent working at a HR ≥ 70% of HR_{max}. Mean predicted HR_{max} for the study participants was 194 ± 1 bpm. Average HR during training was: Visit 1 – 140 ± 10 bpm; Visit 2 – 135 ± 18 bpm; and Visit 3 – 138 ± 17 bpm. There were no significant differences in heart rate responses across visits suggesting that the physiological stimulus of MCMAP sessions are fairly standard across time with the Martial Arts Instructors (MAI) manipulating the training to maintain the physical intensity over time.

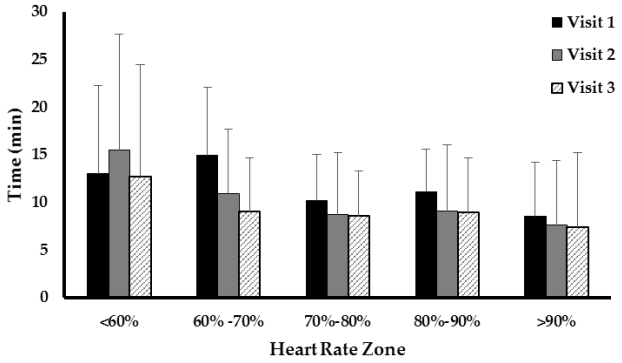

Fig. 1. Time spent in heart rate zones during each of the three training

4.3.2 Responses to training analyzed using serial measurements

Analysis of all blood parameters using serial measurement parallels the HR response with no measures showing any statistical difference across visits. This supports the notion that physical intensity and other stress components are managed within each visit to maintain a given intensity of training no matter the Marine's skill level or combative lesson for that day. Summary results for all measures are presented in Appendix C.

4.3.3 Endocrine responses to training

Characteristic endocrine responses to a military training protocol were observed and included substantial increases in peripheral catecholamines immediately post training. To quantify endocrine responses, both within and between visits, blood parameters were mapped and trend lines visualized. Epinephrine and norepinephrine increased significantly post training with an average increase relative to baseline of 2.8 and 2.4 respectively (Fig. 2). These concentrations decreased rapidly over the recovery period with values at, or near baseline levels by the end of the one-hour recovery period. Cortisol remained relatively stable from pre-to-post training with only a moderate increase observed relative to baseline (1.15). Examination of the random effects values suggests that, as would be expected, higher endocrine concentrations at the Post measure are correlated with a smaller slopes over the recovery period. These data generally indicate standard MCMAP training generates a strong sympathetic adrenal-medullary response with lesser engagement of the hypothalamic-pituitary-adrenal axis. Figures showing endocrine responses over the recovery period along with tables showing the multilevel regression model results can be found in Appendix C.

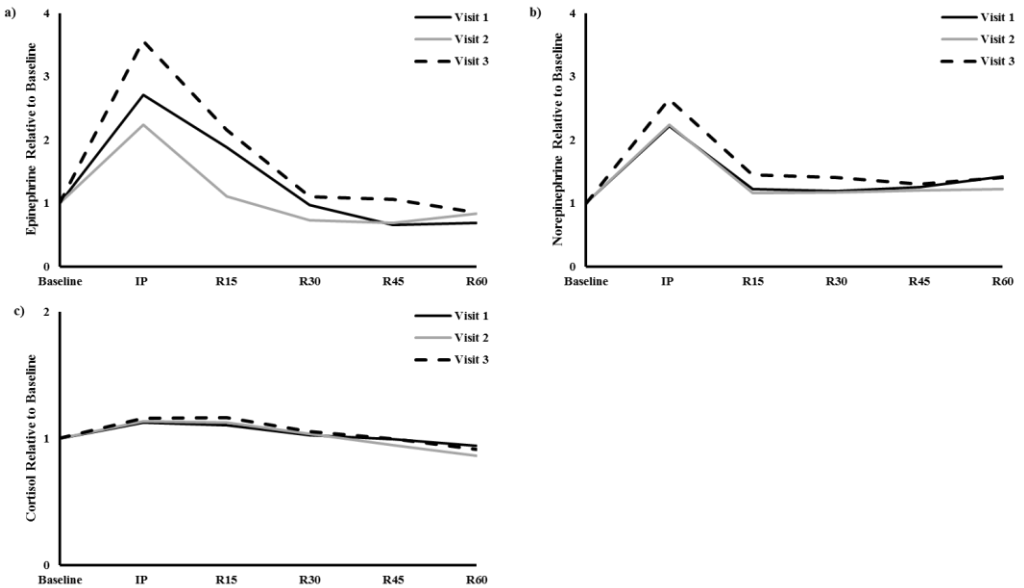

Fig. 2. Fold changes in endocrine concentrations following training sessions. a) Epinephrine, b) Norepinephrine, and c) Cortisol. All values have been normalized to baseline concentrations.

4.3.4 Immune responses to training.

Regarding all the immune variables, every measure examined showed significant change over time during the recovery period. Stereotypical alterations in circulating lymphocytes and leukocytes were observed following MCMAP training sessions with peak peripheral cell counts typically reached immediately post training and then falling below baseline values during the one-hour recovery (Fig. 3).

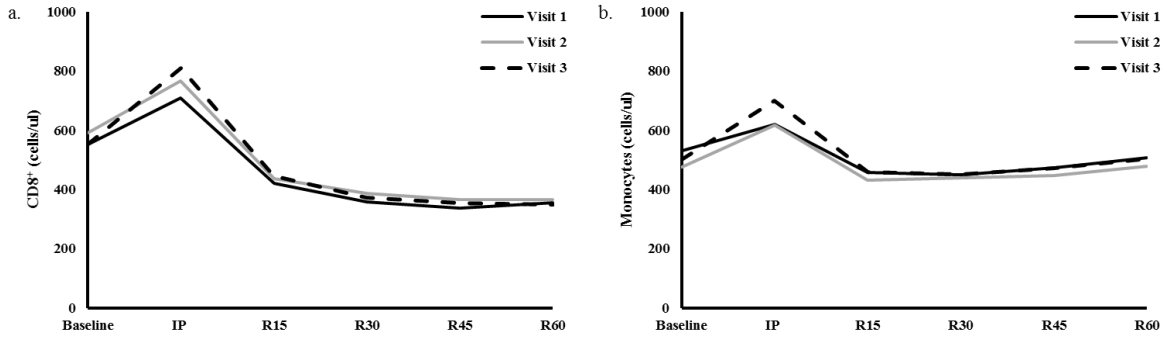

Fig. 3. Representative changes in lymphocyte and leukocyte populations following MCMAP training. a) $CD8^+$ cells, and b) Monocytes.

Changes in the percent of circulating lymphocytes followed characteristic patterns (Fig. 4) with percentages of $CD3^+$, $CD4^+$, and $CD19^+$ cells all increasing over the recovery period. These increases result from the interplay between NK cells, and to a lesser extent $CD8^+$ cells, which peak at the Post measure and subsequently decrease over the one-hour period. The changes in percent of lymphocytes in circulation during the recovery period are, therefore, highly impacted by the initial influence of NK and $CD8^+$ cells.

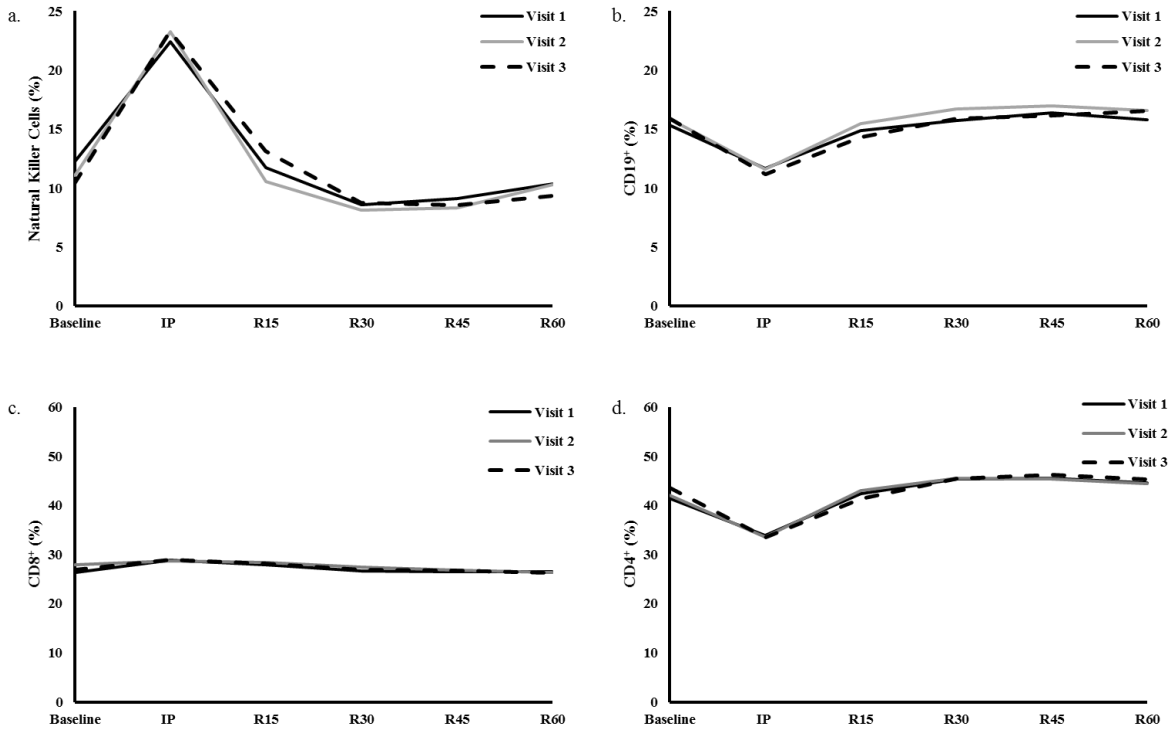

Fig. 4. Percent changes in lymphocyte subsets are driven by increases in circulating Natural Killer and CD8$^+$ cells. a) Natural killer cells, b) CD19$^+$ cells, c) CD8$^+$ cells, and d) CD4$^+$ cells.

Leukocyte counts followed a similar trend with peak values reached at the Post measure with the exception of neutrophils, which continued to increase over the recovery period (Fig. 5). These changes are also reflected in the percent data with circulating neutrophils representing a greater percent of total leukocytes at each time point as other leukocyte measures tended to decline.

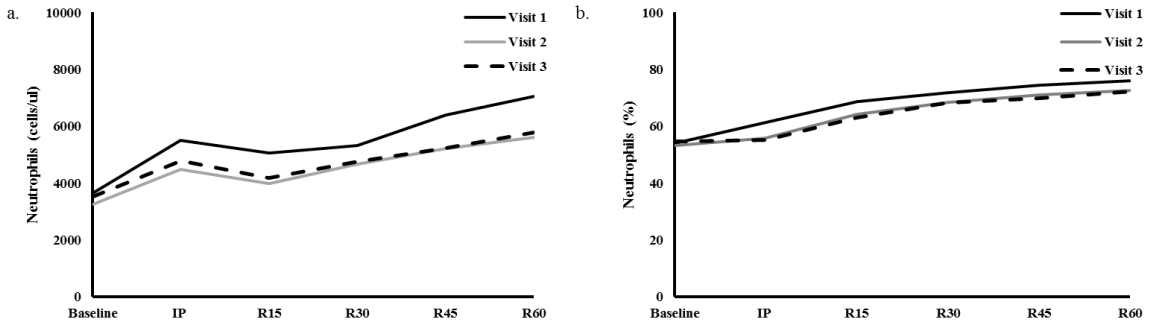

Fig. 5. Characteristic increases in neutrophil cell counts (a) and percent (b) following MCMAP training.

Both immunoglobulins-G and –M showed similar curvilinear trends over the recovery period with peak concentrations observed at the Post measure. Neutrophil oxidative burst capacity showed a very slight increasing trend over the recovery without any real substantial deviation over time. Summary multilevel regression results and figures for all immune parameters are presented in Appendix C.

Chapter 5: Discussion

5.1 Overview

The projects undertaken as part of this research effort were selected to provide a foundation for future work investigating changes in immunocompetence following layered stress challenges. It is evident that impaired immune function can negatively impact an individual, but what is not clear is whether the paradigms used to model high-intensity, layered stress scenarios are appropriate. Additionally, the best methods to assess these changes outside the laboratory have not been determined. The results identified in this project were largely in agreement with our hypotheses regarding stability of T cell surface markers, T cell proliferative responses, and alteration in immune cell circulation following standard U.S. Marine Corps Martial Arts Training. The one exception to these predicted results was the enhanced proliferative response generated by exposure to a high-intensity, layered stress environment.

Functional immune responses to exercise have traditionally been investigated within a highly-controllable laboratory environment and have used immunoendocrine responses induced by various exercise regimens as platforms to generalize results to the stress environments of competitive events or even military wartime operations. Recently, scientists have begun examining paired physical and psychological stressors (dual stress challenges) in laboratory settings with the goal of increasing the veracity of collected data and allowing more accurate generalization of the findings to military and first responder populations operating in tactical situations. While these are excellent models for teasing out the impact of a psychological stressor above that of exercise alone, it is possible that they do not generalize outside of a laboratory setting.

5.2 Delayed analysis negatively influences T cell responses

In light of these considerations we aimed to determine the feasibility of offsite blood collection for the purposes of assessing T cell proliferative capacity in a field environment. The changes we observed comparing both delayed protocols for T cell isolation and different cell stimulating methods suggest that PHA stimulation is more robust to overnight delays in blood processing. This is likely a result of how PHA signals into the cell to initiate T cell proliferation. PHA binds to and subsequently cross-links glycoproteins on the T cell surface; specifically, PHA can cross-link TCR-CD3 complexes allowing for sufficient activation of intracellular signaling (172). This blunt force method of cell activation bypasses the two-signal process required for physiological activation of T cells that is approximated using co-stimulation by CD3+CD28 antibodies. In our study, T cells were isolated from whole blood after an overnight rest in either a room temperature or chilled condition. T cells that were isolated following the overnight delay did not respond as well to co-stimulation by CD3+CD28, suggesting there exists a subtler mechanism for *in vitro* T cell activation and proliferation. More importantly, these findings indicate that the intracellular pathways which exercise may stimulate are sufficiently diminished after an overnight delay that co-stimulation through CD3+CD28 is not the ideal method for analyses of T cell proliferation in this setting. To our knowledge, this is the first study examining the effect of delayed isolation protocols on measures of proliferation and cell activation using different stimulating agents.

5.3 Functional immune responses to layered stressors

The increases in proliferation following a high intensity, layered stress training session were unexpected. We anticipated the intensity and duration of the physical activity would produce a moderate-to-large suppression of proliferative capacity over the recovery period. However, the high-intensity group's increase in proliferative ability is similar to other reports

(139, 141) identified as part of our lab's recent meta-analytic findings (Siedlik, Unpublished), suggesting increased proliferation in high-intensity, competitive environments. These findings indicate there is likely a psychological component involved in this response that is not being detected through our current analytic strategies. In an effort to identify potential mechanisms for the observed proliferative response we investigated a number of relevant immunomodulatory pathways including endocrine measures, cytokine concentrations, and HMGB1.

Differences observed in the endocrine and immunomodulatory responses across high and moderate intensity exercise groups failed to provide a mechanistic target for the observed functional T cell responses. Several studies have observed exacerbated catecholamine responses in veteran firefighters given a work-relevant mental task while cycling at a moderate intensity (60% VO_{2max}) compared to an exercise alone condition (13-15). Similarly increased concentrations of cortisol have been observed in firefighter and civilian populations undergoing analogous dual stress challenges (15, 16, 158). Most relevant to the present work, applications of dual stress challenges compared to exercise alone, have observed increased immune cell trafficking, markers of oxidative stress, and alterations immunomodulatory cytokines (13, 14, 159).

The significant difference in peripheral TNF-α concentrations across the groups is probably derived from increased secretions by skeletal muscle. Muscle has been widely accepted as a potent endocrine organ during high intensity exercise (173) and not only explains group difference based on physical intensity level but also addresses the relatively low increases (~1.5 fold change) in the circulation. This finding is mirrored by the peripheral IL-6 response (~1.6 fold change) and suggests these measures are representative of changes in skeletal muscle inflammatory processes and not necessarily derived from immune cell activity.

The IL-10 response observed in the high intensity group (~22.6 fold change) is strongly indicative of a negative feedback mechanism aimed at inhibiting T cell proliferation in these subjects. IL-10 is known to indirectly regulate T cell functional responses via a direct effect on monocytes and macrophages (174). IL-10 inhibits costimulatory molecules B7-1 and B7-2 and MHC Class II expression on monocytes and macrophages thereby subverting the second-signal mechanism required for cell proliferation (175). Further, IL-10 can directly inhibit the tyrosine phosphorylation of CD28 and subsequent PI3K binding in T cells, inhibiting production of a number of immunomodulatory cytokines including IFN-γ, IL-2, IL-4, IL-5, and TNF-α (175, 176). To this end, the large scale increases observed in all high intensity group participants may be a physiological response to prevent an overshoot in the proliferative immune response.

During the recovery portion, the observed IL-10 response is probably in rebuttal to a significant inflammatory and/or proliferative response during the training session that we were unable to quantify without an in-session blood measure. An in-session measure would potentially clarify the cytokine data as well. Due to the variations in the half-life of these signaling proteins and the interplay between them, the data presented here may not be representative of the initial insult to the physiological system but instead approximate the body's attempt to mitigate the stress response and return to homeostasis following the primary stress exposure. Unfortunately we were unable to identify a potential mechanism for enhanced proliferation. Differences in measured endocrine parameters are trivial enough to preclude those as being likely mediators for increased proliferation. Similarly, the observed cytokine profiles limit any hypotheses toward cytokine-mediated cell signaling.

Our hypothesis that increased oxidative stress may cause greater expression of damage associated molecular pattern (DAMP) molecules that subsequently stimulates lymphocyte

proliferation was also not borne out in our observed data. The oxidative stress response to exercise is similar to lymphocyte trafficking in that it is heavily influenced by exercise intensity and duration. The majority of endogenous reactive oxygen species (ROS) are produced in the mitochondrial electron transport chain (177). Studies have shown diminished markers of oxidative stress at moderate intensity with both high intensity aerobic and anaerobic exercise showing elevated markers of oxidative stress in comparison (178). Regardless of the stimulant, increased concentration of ROS can lead to macromolecular damage and impairments of cellular function (179).

HMGB1 is secreted by macrophages and dendritic cells in response to increased oxidative stress. Moreover, mitochondrial HMGB1 expression is increased in response to oxidative stress (179). HMGB1 is one of the prototypical DAMPs and has been shown to increase proliferation of activated $CD4^+$ and $CD8^+$ cells in culture (180). In this study we did not observe any substantial HMGB1 concentration differences between groups suggesting it is likely not initiating the increases in proliferation. Although it has been presented here in a very simplistic model, HMGB1 is a redundant molecule and other DAMPs released in response to oxidative stress such as S100 proteins and heat shock proteins may serve in the same mechanistic roles (181). Again, we anticipate future work will examine other DAMPs and variations in not only the level of stress but also differences in fitness levels as way to illuminate possible mechanisms for enhanced signaling.

On a macro level, the main findings from the first two studies suggest that the exercise models currently utilized to approximate stressful environments are probably insufficient for modeling the physiologic response. This, therefore, defines the primary impetus for Project Three, which provides a specific accounting of the physiologic immunoendocrine response to

standardized U.S. Marine Corps training. As identified by the heart rate data recorded, MCMAP is not a tremendously stressful training environment but does provide an accurate assessment of the physiological response to real-life training, which we believe is the next evolution of dual-challenge stress research in a field environment. It is important to note that the heart rate responses observed within MCMAP sessions are similar to those measured in laboratory based dual stress challenge testing (13-16, 158, 159, 164). Similarly, observed endocrine measures from MCMAP training closely resemble both the catecholamine (13-15) and cortisol responses (15, 16, 158) identified in subjects undergoing dual stress challenges.

Lymphocyte redistribution following MCMAP is similar to that shown in research examining lymphocyte subset trafficking in firefighters participating in paired exercise and computer-based simulations (13). Together these would suggest that the general framework of current MCMAP training is a real-world analogue of laboratory based dual stress research protocols. To date, no research has yet examined leukocyte redistribution trends following dual stress challenges and we anticipate our data will provide a more complete profile of the immunoendocrine response following training and exposure to combined stress environments.

In two studies by Huang, *et al*. (14, 159), IL-2 responses have been examined as part of the immune response to laboratory based dual stress challenges with conflicting results. Our full analyses of immunoendocrine responses to MCMAP training did not account for changes in cytokine concentrations following training. However, earlier work from our lab investigating a single bout of MCMAP training did not find a significant IL-2 response (165). Taken together, we propose that the library of response curves we have developed for immunoendocrine parameter changes following standard U.S. Marine Corps training adequately quantify the effects of dual stress challenges in a field environment.

In our analyses, we benefited from the uniformity of the subjects training status. They had roughly the same age and anthropomorphic characteristics, they were at the same point in their training pipeline (i.e. beginning formal military occupational specialty [MOS] training) and they adhered to a fairly standard training protocol for the roughly 17 weeks prior to enrolling in this study. This allows for interpreting the data within the context of newly enlisted, male Marines entering formal MOS training. The regression equations derived from these data will serve as a foundation for modeling stress responses and provide for identification of novel training environments, both in laboratory and field settings that generate significantly different immunoendocrine recovery profiles. Moreover, this data set will provide a base from which future research can assess deviations in stress responses that may results from advanced training or experience on operational deployments.

5.4 Conclusions

In summation, the evidence presented here suggests a methodological outline for best practices regarding field assessments of immune function where isolation of T cells from whole blood may be delayed due to logistical constraints. Further, we submit that variations in exercise intensity and duration do not necessarily approximate military operational or tactical stress responses. The time course for immunoendocrine responses to stressors of this nature will need to be further assessed to ascertain the functional changes occurring at the time of stress onset.

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Appendix A: T Cell Proliferation and Activation Following Exercise

Table 1. Measures of T cell proliferation. Values are presented as Mean ± SD.

Proliferation			Cell Count						Percent					
			Pre			Post			Pre			Post		
No Stim	SP	CT	1224	±	617	1303	±	909	2.4	±	1.6	1.6	±	0.9
		EX	941	±	1000	941	±	774	0.8	±	0.5	1.0	±	0.7
	RT	CT	1644	±	1754	1182	±	856	2.1	±	2.4	1.7	±	0.8
		EX	455	±	300	779	±	647	0.7	±	0.8	0.8	±	0.6
	CH	CT	2537	±	2504	1360	±	714	2.1	±	1.7	1.6	±	0.9
		EX	518	±	317	593	±	331	0.7	±	0.4	0.8	±	0.5

Proliferation			Cell Count						Percent					
			Pre			Post			Pre			Post		
CD3+CD28	SP	CT	49727	±	60006	47906	±	54041	32.4	±	23.8	31.2	±	19.2
		EX	89050	±	39987	115394	±	57251	44.5	±	20.9	60.1	±	15.6
	RT	CT	44400	±	23299	48547	±	55691	33.0	±	16.1	32.4	±	21.3
		EX	50097	±	62762	37365	±	25624	26.0	±	20.1	34.0	±	17.5
	CH	CT	68331	±	61640	70565	±	55141	34.0	±	20.4	40.9	±	23.8
		EX	50958	±	44451	48314	±	34881	32.5	±	14.7	36.3	±	18.8

Proliferation			Cell Count						Percent					
			Pre			Post			Pre			Post		
PHA	SP	CT	9689	±	16355	7342	±	11557	16.0	±	27.3	12.6	±	22.5
		EX	14835	±	18713	31165	±	25473	31.2	±	29.2	43.0	±	34.2
	RT	CT	19095	±	34844	4475	±	3607	17.4	±	29.2	9.3	±	12.5
		EX	7952	±	8453	29095	±	30501	21.0	±	17.5	38.7	±	36.5
	CH	CT	15685	±	25787	22160	±	39668	21.3	±	25.2	17.0	±	26.9
		EX	7240	±	9783	25249	±	32467	26.2	±	23.7	34.8	±	29.7

Table 2. Measures of T cell activation ($CD4^{-}CD25^{+}$).

Activation			Cell Count						Percent					
			Pre			Post			Pre			Post		
No Stim	SP	CT	1950	±	2707	1643	±	1280	2.3	±	2.6	2.1	±	1.6
		EX	4261	±	5358	6603	±	8035	3.2	±	3.2	5.9	±	7.2
	RT	CT	1833	±	1552	1267	±	803	2.2	±	1.8	1.7	±	0.8
		EX	1180	±	756	2063	±	2871	1.3	±	0.8	2.6	±	3.3
	CH	CT	1689	±	1203	1830	±	2018	1.6	±	1.1	1.6	±	1.4
		EX	830	±	529	2591	±	3498	1.0	±	0.6	2.3	±	2.2

Activation			Cell Count						Percent					
			Pre			Post			Pre			Post		
CD3+CD28	SP	CT	46782	±	48541	48928	±	40535	33.3	±	17.9	35.9	±	12.6
		EX	85968	±	35436	105742	±	54577	43.8	±	20.2	54.2	±	19.5
	RT	CT	40173	±	17970	44122	±	44198	30.0	±	11.4	31.6	±	16.4
		EX	42169	±	46624	34334	±	24292	25.1	±	14.3	29.8	±	20.0
	CH	CT	63811	±	56640	49396	±	37010	32.5	±	16.7	34.2	±	17.1
		EX	32841	±	26183	47240	±	31737	32.1	±	13.6	36.4	±	18.1

Activation			Cell Count						Percent					
			Pre			Post			Pre			Post		
PHA	SP	CT	6041	±	4865	6645	±	3721	8.1	±	6.0	9.7	±	6.6
		EX	7178	±	6955	13829	±	9762	14.7	±	10.0	18.3	±	13.3
	RT	CT	8893	±	10183	4625	±	3872	8.9	±	8.2	7.1	±	3.7
		EX	3360	±	2963	10510	±	11214	9.4	±	5.1	13.5	±	13.1
	CH	CT	6993	±	6499	10502	±	8010	10.7	±	6.0	8.8	±	4.9
		EX	2949	±	2414	13754	±	13987	10.5	±	5.5	14.8	±	10.9

Table 3. Measures of T cell activation ($CD4^+CD25^+$).

Activation			Cell Count						Percent					
			Pre			Post			Pre			Post		
No Stim	SP	CT	14992	±	13065	15676	±	6942	20.0	±	9.8	20.1	±	7.6
		EX	26711	±	25483	25408	±	24008	21.2	±	12.9	23.3	±	18.1
	RT	CT	14550	±	7637	11727	±	7159	17.3	±	8.5	15.2	±	3.3
		EX	11356	±	6974	12100	±	13649	11.9	±	3.9	16.0	±	15.6
	CH	CT	17524	±	9296	16560	±	12537	15.2	±	6.5	15.7	±	7.5
		EX	18324	±	19666	13502	±	11906	11.6	±	3.1	14.1	±	8.6

Activation			Cell Count						Percent					
			Pre			Post			Pre			Post		
CD3+CD28	SP	CT	31358	±	33131	31150	±	22404	22.8	±	6.9	22.5	±	5.6
		EX	42626	±	19611	40973	±	22563	21.0	±	5.1	21.1	±	6.7
	RT	CT	28102	±	13312	27605	±	23307	21.8	±	8.4	21.7	±	5.1
		EX	27324	±	30382	16089	±	12597	17.5	±	6.9	17.6	±	8.6
	CH	CT	41882	±	29456	43889	±	30807	21.8	±	8.9	25.8	±	11.3
		EX	28237	±	19728	24201	±	14622	20.1	±	4.0	19.8	±	4.2

Activation			Cell Count						Percent					
			Pre			Post			Pre			Post		
PHA	SP	CT	20756	±	10886	22656	±	6323	31.5	±	15.3	29.8	±	17.2
		EX	19854	±	11722	33412	±	17139	42.9	±	17.4	43.7	±	23.3
	RT	CT	26410	±	23865	15871	±	8820	27.8	±	18.0	27.3	±	14.8
		EX	12734	±	6763	28593	±	20596	38.4	±	14.0	38.3	±	25.1
	CH	CT	22904	±	19407	33301	±	34891	35.5	±	19.5	31.2	±	20.0
		EX	11610	±	4633	24614	±	10882	43.1	±	15.0	44.4	±	17.5

Table 4. Cell Viability (%).

			Pre			Post		
No Stim	SP	CT	41.5	±	20.8	49.4	±	17.4
		EX	54.5	±	10.3	48.3	±	11.0
	RT	CT	47.1	±	12.3	45.2	±	15.6
		EX	42.7	±	11.8	39.6	±	8.0
	CH	CT	51.0	±	11.4	50.7	±	12.9
		EX	41.4	±	11.7	38.9	±	12.0

			Pre			Post		
CD3+CD28	SP	CT	37.8	±	10.5	38.6	±	10.9
		EX	38.8	±	8.7	32.7	±	8.2
	RT	CT	44.4	±	6.8	41.4	±	9.0
		EX	35.0	±	10.6	29.8	±	12.2
	CH	CT	37.3	±	8.7	36.7	±	13.2
		EX	33.4	±	9.5	29.2	±	11.2

			Pre			Post		
PHA	SP	CT	38.4	±	16.2	41.2	±	12.1
		EX	29.6	±	15.7	28.3	±	9.4
	RT	CT	45.8	±	10.6	39.6	±	17.3
		EX	19.5	±	8.6	24.0	±	9.9
	CH	CT	42.8	±	15.0	45.4	±	10.8
		EX	21.3	±	10.7	24.5	±	9.9

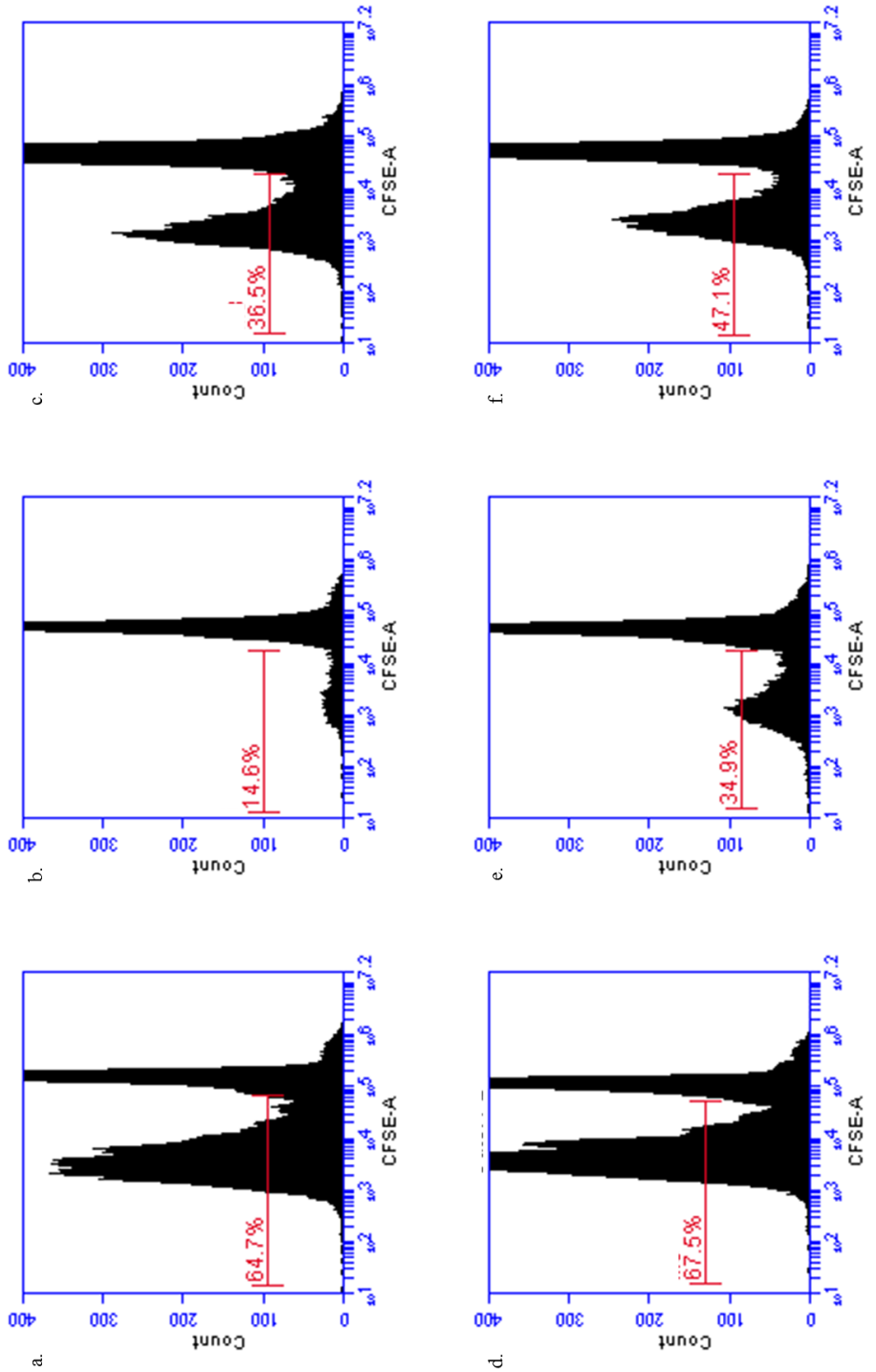

Fig.1. Representative flow plots for T cell proliferation following exercise. All T cells were stimulated with CD3+CD28. a) Pre SP, b) Pre RT, c) Pre CH, d) Post SP, e) Post RT, and f) Post CH. SP: Standard Protocol; RT: Rested overnight in whole blood at room temperature; CH: Rested overnight in whole blood at 4°C.

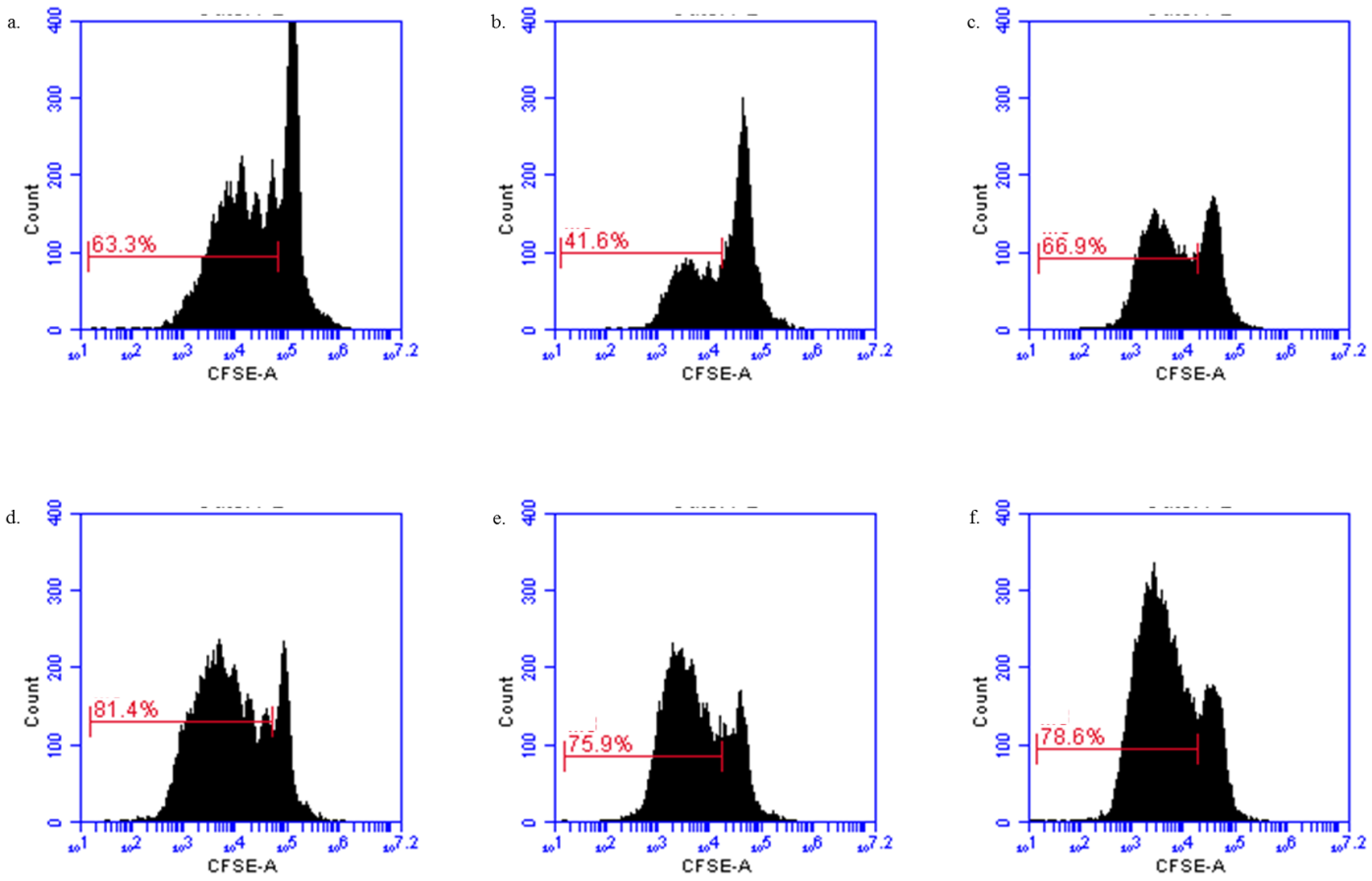

Fig.2. Representative flow plots for T cell proliferation following exercise. All T cells were stimulated with PHA. a) Pre SP, b) Pre RT, c) Pre CH, d) Post SP, e) Post RT, and f) Post CH. SP: Standard Protocol; RT: Rested overnight in whole blood at room temperature; CH: Rested overnight in whole blood at 4˚C.

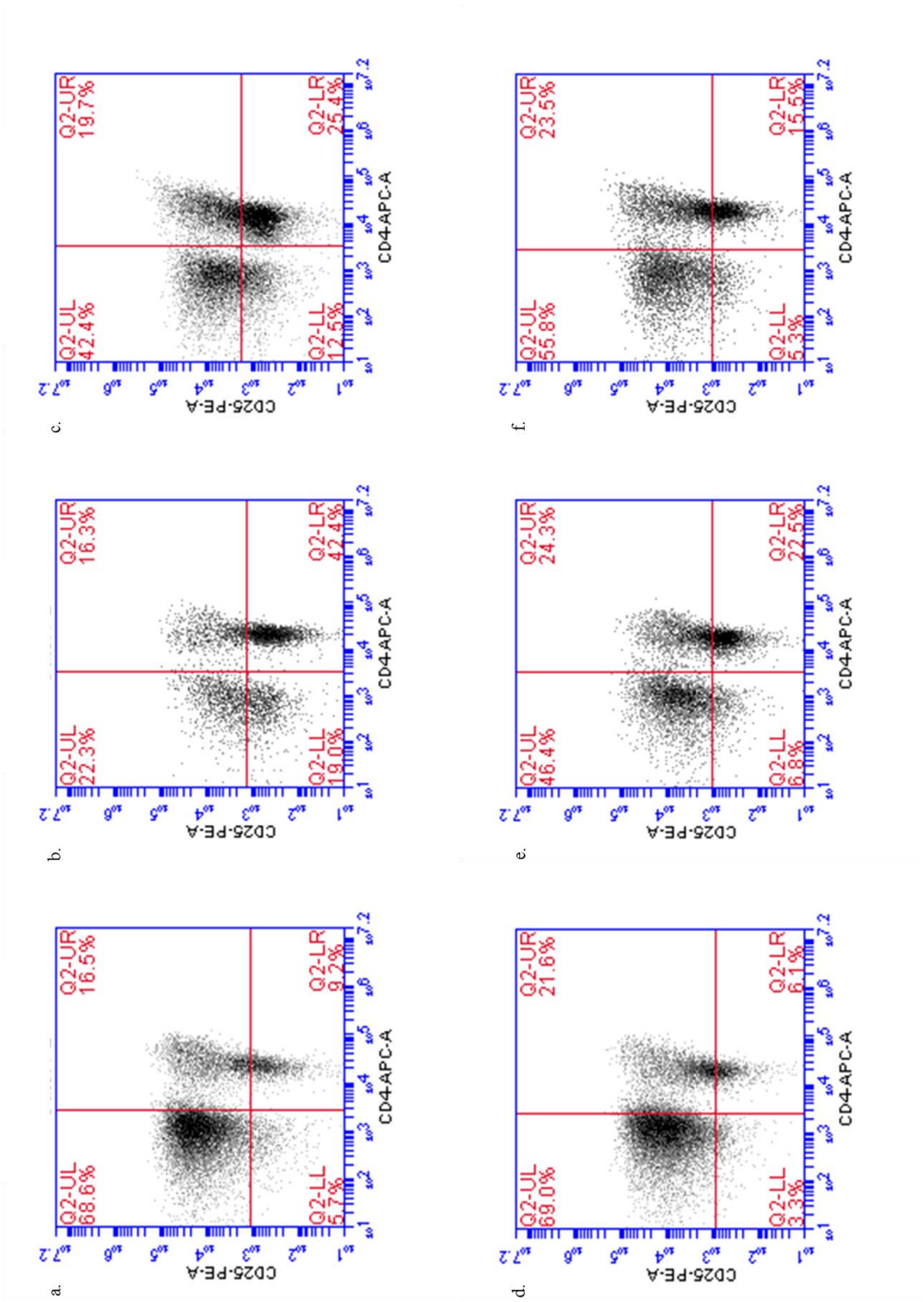

Fig. 3. Representative flow plots for T cell activation following exercise. All T cells were stimulated with CD3+CD28. a) Pre SP, b) Pre RT, c) Pre CH, d) Post SP, e) Post RT, and f) Post CH. SP: Standard Protocol; RT: Rested overnight in whole blood at room temperature; CH: Rested overnight in whole blood at 4˚C.

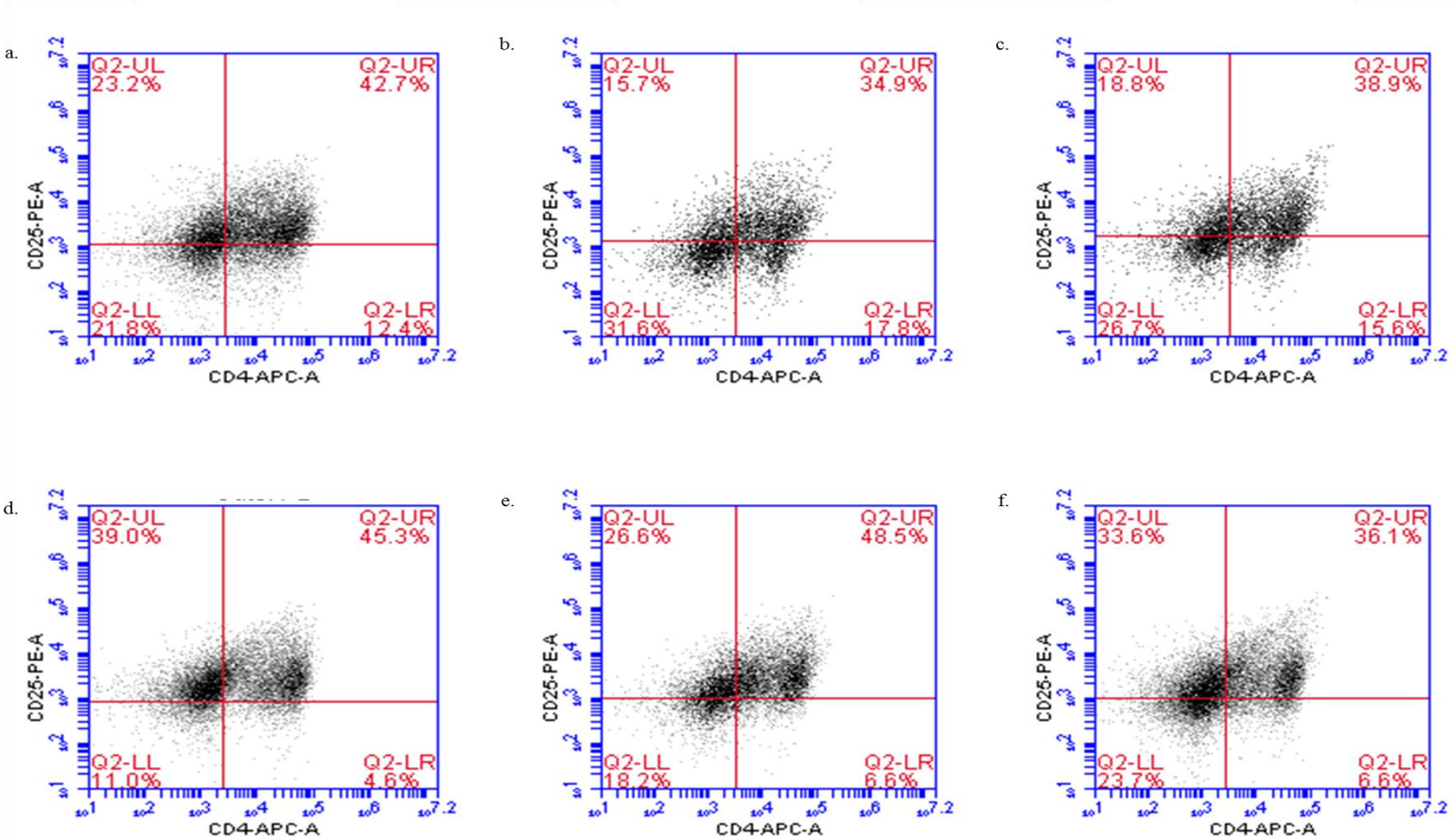

Fig.4. Representative flow plots for T cell activation following exercise. All T cells were stimulated with PHA. a) Pre SP, b) Pre RT, c) Pre CH, d) Post SP, e) Post RT, and f) Post CH. SP: Standard Protocol; RT: Rested overnight in whole blood at room temperature; CH: Rested overnight in whole blood at 4˚C.

Control Proliferation Count (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	1076	2055	703	603	1030	847
S2	1579	437	5061	474	3130	2111
S3	744	1407	1342	2564	7336	1935
S4	1921	2383	1789	1394	1554	907
S5	1700	1495	416	1669	1587	1926
S6	321	39	550	386	583	431

Control Proliferation Count (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	9161	17509	53259	4520	10486	22704
S2	23213	7854	62987	15768	159651	88537
S3	3216	23290	3951	7957	9954	5403
S4	147258	61953	39064	92754	72522	144422
S5	13880	25211	38445	29396	35836	44669
S6	101635	151616	68695	140884	121536	117654

Control Proliferation Count (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	1181	1555	1365	1522	4184	2811
S2	6353	3018	9936	447	5206	1460
S3	4022	3779	3548	2694	6472	1953
S4	1451	2406	3400	7711	4060	22120
S5	2285	2407	6361	4873	5903	3118
S6	42843	30885	89961	9603	68287	101495

Control Proliferation % (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	4.2	2.3	1.5	2	1.9	1.7
S2	4.4	2.2	6.9	1.6	2.4	3
S3	2.4	1.3	1.3	3	5.3	1.8
S4	1.2	2.4	1.8	1.6	1.5	0.8
S5	1.9	1.4	0.4	1.2	1.1	1.7
S6	0.3	0.1	0.7	0.5	0.5	0.3

Control Proliferation % (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	20.8	15.7	44.4	9.4	14.9	27.5
S2	32.8	27.1	40.5	31.2	52.8	57
S3	4.2	19.7	5.7	10	9.2	3.7
S4	53.8	39.1	30.2	46.3	39.2	56.5
S5	15.9	19.2	26.2	32.7	28	33.4
S6	66.8	66.5	50.8	64.8	60.1	67.5

Control Proliferation % (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	10	3.8	2.9	4.1	8.7	6.1
S2	5.6	4.3	7	1.9	28.7	2.7
S3	3.2	2.9	7.4	2.7	5.4	2
S4	1.8	3.3	3.9	8.5	7.7	16.7
S5	3.9	3	6.4	4.2	7.5	3.6
S6	71.5	58.5	76.9	34.4	69.5	70.7

Exercise Proliferation Count (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	247	178	144	1082	1018	174
S2	1006	484	865	1103	500	484
S3	547	778	798	1775	523	652
S4	518	629	345	146	145	359
S5	412	2355	275	220	694	777
S6	2916	1222	302	345	230	1110

Exercise Proliferation Count (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	107800	100855	121018	34582	127207	74223
S2	106867	167783	10922	36000	18671	25922
S3	8657	20289	1214	2476	3393	1317
S4	102327	178203	139648	47349	71200	43990
S5	93844	98000	6825	24194	52944	44462
S6	114807	127231	20954	79590	32333	99972

Exercise Proliferation Count (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	409	1659	482	955	2536	9282
S2	6205	33584	1629	2897	3910	20009
S3	1051	2693	1445	1468	630	1147
S4	4830	31027	11912	47223	6641	3240
S5	31889	60771	22037	56330	26802	87691
S6	44625	57257	10208	65697	2923	30127

Exercise Proliferation % (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	0.3	0.2	0.1	1.1	0.7	0.2
S2	1.2	0.9	1.3	1.1	1.1	0.6
S3	0.7	1.2	2.1	1.8	1	1.4
S4	0.5	0.6	0.2	0.3	0.2	0.6
S5	0.4	2.2	0.2	0.3	0.6	0.5
S6	1.7	0.9	0.4	0.4	0.3	1.3

Exercise Proliferation % (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	38.6	58.6	50.7	26.2	46.1	33.8
S2	62.5	75.5	13.8	40.3	30.4	36.4
S3	7.1	30.4	2.4	4.1	5	3.5
S4	46.5	66.3	49.9	44	43.7	36.7
S5	64.7	67.5	14.6	34.1	36.5	47.1
S6	47.7	62.1	24.3	55.1	33.2	60.1

Exercise Proliferation % (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	0.5	1.4	2.9	2.1	6.3	11.6
S2	18.2	39	12.4	12.5	36.7	44
S3	1.9	3.8	2.4	2.2	1.1	1.8
S4	36.9	61.9	28.1	69.1	22.8	16.5
S5	63.3	81.4	41.6	73.3	66.9	78.6
S6	66.4	70.3	38.8	73	23.2	56

Control $CD4^{-}CD25^{+}$ (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	248	2523	1268	733	1394	625
S2	461	287	401	250	897	469
S3	273	379	981	1009	1055	449
S4	1253	1186	1128	1201	1036	1518
S5	2209	1917	2574	2018	1678	2229
S6	7256	3565	4643	2393	4074	5688

Control $CD4^{-}CD25^{+}$ (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	8705	23574	47046	5585	13375	20746
S2	29595	12631	56625	17375	159651	36953
S3	5152	26972	5652	9490	8550	5403
S4	127714	62444	38342	97427	62871	104045
S5	26256	44385	43790	32504	44727	48990
S6	83271	123560	49585	102353	93690	80236

Control $CD4^{-}CD25^{+}$ (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	459	2165	2872	2188	5883	4114
S2	12821	11925	4572	1003	2394	11949
S3	4756	5577	1093	2166	2736	1787
S4	2769	3937	4809	9081	3847	15879
S5	4316	6086	11666	9954	7429	6309
S6	11127	10178	28343	3356	19666	22971

Control CD4+CD25+ (%) (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	14.3	15.3	18.7	15.9	14.8	14.2
S2	17.4	22	10.6	11.4	10.1	11.5
S3	16.5	12.5	11.8	12.2	11.8	8.9
S4	12.2	17.6	12.1	14.6	12.1	13.7
S5	20.4	19.1	17.3	16.6	14.2	15.5
S6	39.2	34.1	33.4	20.4	28	30.1

Control CD4+CD25+ (%) (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	18	17.2	25.1	15.4	17.8	19.6
S2	17.6	20.7	17.9	19.6	27.1	23.8
S3	16.8	16	13.9	17.8	15.2	10.9
S4	34.8	27.6	16.1	24.5	12.1	35
S5	24	23	20.5	23.7	22	23
S6	25.6	30.2	37	29.4	36.4	42.5

Control CD4+CD25+ (%) (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	36.3	32.6	27.9	22.4	28.2	28.1
S2	19	27.2	15.3	20.3	57.1	21.8
S3	22.6	4.2	14.3	14.9	16.1	13.3
S4	23.1	29.8	21.8	25.4	23	31.7
S5	27.6	27.1	24.4	24.3	25.4	22.4
S6	60.3	58	62.8	56.5	62.9	70.1

Exercise $CD4^{-}CD25^{+}$ (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	349	982	775	282	1405	275
S2	788	356	730	79	300	335
S3	537	18	154	799	185	423
S4	3083	6333	2063	1013	701	1310
S5	6834	20056	1394	2559	981	9074
S6	13972	11870	1964	7645	1405	4128

Exercise CD4-CD25+ (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	92336	87048	109291	26882	11513	70768
S2	104879	157898	16765	23390	17774	24240
S3	14428	11748	1347	3600	4540	2312
S4	97654	158425	93435	43045	66254	42796
S5	99513	100110	10467	32888	61504	52657
S6	107000	119222	21706	76200	35462	90669

Exercise CD4-CD25+ (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	3118	7573	800	734	3364	23009
S2	3881	15916	1194	642	1288	6336
S3	2883	956	1322	1851	1137	2871
S4	2089	10726	5294	12842	2827	1511
S5	11674	29135	8333	20477	7528	37485
S6	19423	18666	3217	26513	1552	11313

Exercise CD4+CD25+ (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	9091	8914	10045	1364	16603	5027
S2	9521	5319	4840	1224	57554	4168
S3	10311	417	3328	8722	3619	5380
S4	28342	37083	22136	9730	9506	9768
S5	27623	40345	15550	13394	11222	32203
S6	75379	60370	12239	38163	11440	24467

Exercise CD4+CD25+ (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	51818	33373	43182	19736	64333	39178
S2	33385	43891	9175	9872	14835	13617
S3	20561	6716	5142	8680	8630	5530
S4	56636	69370	82416	2541	32536	21259
S5	23908	31348	7633	17212	28614	22157
S6	69449	61138	16394	38490	20472	43467

Exercise CD4+CD25+ (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	16881	26310	5300	12431	15127	21572
S2	17238	48542	4927	5818	5798	23899
S3	14142	6137	11227	13741	10104	15271
S4	7518	31251	21107	47394	16175	12224
S5	21490	33828	18509	37284	15573	40242
S6	41852	54401	15334	54889	6883	34477

Exercise $CD4^{-}CD25^{+}$ (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	0.4	1.3	0.8	0.1	1	0.3
S2	1	0.6	1.1	0.1	0.6	0.4
S3	0.7	0	0.4	0.8	0.3	0.9
S4	2.7	6.1	1.4	2	0.9	2.1
S5	6.1	18.7	1.2	3.7	0.9	5.3
S6	8.1	8.8	2.8	8.6	2	4.7

Exercise $CD4^{-}CD25^{+}$ (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	33	50.5	45.8	7.3	41.7	32.2
S2	61.3	71	21.2	26.2	28.9	34
S3	11.8	17.6	2.7	6	6.7	6.1
S4	44.4	58.9	33.4	40	40.7	35.8
S5	68	69	22.3	46.4	42.4	55.8
S6	44.4	58.2	25.2	52.8	32.2	54.5

Exercise $CD4^{-}CD25^{+}$ (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	3.5	6.5	4.7	0.3	8.4	8
S2	11.4	18.5	9.1	2.8	12.1	13.9
S3	5.2	1.4	2.2	2.7	1.9	4.6
S4	15.9	21.4	12.5	18.8	9.7	7.7
S5	23.2	39	15.7	26.6	18.8	33.6
S6	28.9	22.9	12.2	29.5	12.3	21

Exercise $CD4^+CD25^+$ (%) (non stim)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	9.2	11.6	10.4	0.5	12.1	5.4
S2	11.5	9.5	7.1	1.2	12.2	5.4
S3	13.1	0.7	8.8	13	6.6	11.5
S4	25.2	35.5	14.8	19.2	12.1	15.3
S5	24.6	37.6	13	19.1	10.3	18.9
S6	43.5	44.6	17.5	42.9	16	27.9

Exercise $CD4^+CD25^+$ (%) (3+28)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	18.5	19.4	18.1	5.4	23.3	17.8
S2	19.5	19.7	11.6	11.1	24.1	19.1
S3	16.8	10.1	10.2	14.5	12.7	14.6
S4	25.8	25.8	29.5	23.7	20	17.8
S5	16.5	21.6	16.3	24.3	19.7	23.5
S6	28.8	29.9	19	26.7	21	26.1

Exercise $CD4^+CD25^+$ (%) (PHA)

	Pre	Post	Pre.RT	Post.RT	Pre.CH	Post.CH
S1	18.8	22.5	31.5	5.5	37.7	27.1
S2	50.5	56.4	37.5	25.2	54.4	52.5
S3	25.6	8.7	18.3	20.3	17.2	24.5
S4	57.4	62.3	49.8	69.3	55.5	62.2
S5	42.7	45.3	34.9	48.5	38.9	36.1
S6	62.2	66.8	58.2	61	54.6	64.1

	Heart Rate (EX)		Time (min) in Heart Rate Zones				
Subject	Peak	Average	<60% MHR	60-70% MHR	70-80% MHR	80-90% MHR	>90% MHR
S1	187	132	5.5	6.0	14.6	3.7	1.9
S2	194	159	2.1	4.3	6.5	3.8	15.2
S3	237	157	5.4	3.2	5.7	3.4	15.0
S4	203	167	2.1	0.4	7.0	7.8	15.3
S5	192	129	12.7	4.7	2.9	6.8	1.9
S6	183	154	0.2	2.5	10.2	12.7	5.7

	Heart Rate (CT)	
Subject	Peak	Average
S1	108	75
S2	80	74
S3	95	86
S4	104	79
S5	101	72
S6	108	89

Appendix B: Do Military and Tactical Experiences Model the Characteristic Exercise Response

Table 1. Endocrine responses to training. Values are presented as Mean ± SD.

	Pre	Post	1hr	4hr	6hr
Cortisol (mg/dl)					
HI	20.26 ± 2.90	26.17 ± 3.92	20.33 ± 4.69	9.34 ± 4.04	7.66 ± 1.67
MOD	18.46 ± 2.50	18.37 ± 6.37	16.87 ± 8.41	9.44 ± 1.40	8.78 ± 3.55
Epinephrine (pg/ml)					
HI	49.74 ± 23.52	108.94 ± 49.43	81.99 ± 52.46	43.74 ± 14.33	45.48 ± 31.18
MOD	51.51 ± 26.33	113.22 ± 61.39	63.27 ± 33.37	58.79 ± 33.37	61.42 ± 33.23
Norepinephrine (pg/ml)					
HI	1058.44 ± 642.28	3047.65 ± 3099.98	1725.95 ± 1482.69	1819.92 ± 1875.98	1549.07 ± 1312.11
MOD	1278.67 ± 856.76	2012.18 ± 1393.07	1685.20 ± 1639.15	1152.12 ± 830.04	1054.75 ± 931.57

Table 2. Creatine kinase and cytokine responses to training. Values are presented as Mean ± SD.

	Pre	Post	1hr	4hr	6hr
Creatine Kinase (AU)					
HI	409.09 ± 388.02	594.28 ± 372.93	770.81 ± 508.28	759.07 ± 518.11	807.68 ± 438.25
MOD	692.53 ± 655.67	651.54 ± 527.08	760.92 ± 418.08	1017.38 ± 625.00	1088.44 ± 687.46
IL-1b (pg/ml)					
HI	1.99 ± 3.85	1.99 ± 3.73	1.79 ± 3.48	1.82 ± 3.42	1.83 ± 3.44
MOD	2.89 ± 5.96	3.51 ± 7.27	3.25 ± 6.61	3.61 ± 5.73	3.26 ± 6.32
IL-2 (pg/ml)					
HI	3.38 ± 7.16	4.61 ± 9.24	3.50 ± 7.54	3.32 ± 6.87	3.63 ± 7.78
MOD	3.58 ± 7.19	4.26 ± 8.82	3.76 ± 7.63	4.33 ± 7.07	3.73 ± 7.37
IL-4 (pg/ml)					
HI	8.65 ± 18.93	11.90 ± 23.01	12.00 ± 24.84	9.40 ± 19.98	10.22 ± 21.05
MOD	16.75 ± 33.39	19.07 ± 40.96	18.06 ± 36.84	18.57 ± 31.48	16.21 ± 33.22
IL-6 (pg/ml)					
HI	5.41 ± 15.30	12.70 ± 19.79	8.52 ± 17.06	5.06 ± 14.31	6.26 ± 17.71
MOD	2.82 ± 4.12	3.35 ± 4.79	4.86 ± 8.71	6.13 ± 11.98	3.52 ± 7.24
IL-10 (pg/ml)					
HI	8.84 ± 14.06	111.59 ± 83.69	58.97 ± 59.19	9.70 ± 14.92	9.41 ± 14.52
MOD	18.59 ± 28.51	13.86 ± 21.97	12.55 ± 20.68	37.17 ± 77.70	32.97 ± 64.55
IL-17a (pg/ml)					
HI	17.19 ± 23.30	29.58 ± 32.52	22.24 ± 29.50	18.85 ± 23.92	20.10 ± 26.25
MOD	13.68 ± 28.81	7.42 ± 14.03	18.87 ± 52.14	16.72 ± 44.31	11.15 ± 31.52
IFN-g (pg/ml)					
HI	38.64 ± 64.53	71.04 ± 107.86	52.47 ± 99.66	39.93 ± 73.85	48.92 ± 97.84
MOD	31.39 ± 64.42	16.57 ± 30.69	47.10 ± 126.11	53.50 ± 135.59	27.48 ± 71.55
TNF-a (pg/ml)					
HI	14.59 ± 8.91	23.75 ± 14.51	18.88 ± 9.56	14.66 ± 8.24	13.69 ± 7.50
MOD	13.03 ± 7.76	10.54 ± 5.90	10.45 ± 5.16	13.03 ± 7.89	12.67 ± 7.23

Table 3. HMGB1, Proliferation and CTLA4 measures. Data are presented as Means ± SD.

	Pre	Post	1hr	4hr	6hr
HMGB1 (ng/ml)					
HI	19.06 ± 5.73	20.14 ± 7.64	19.47 ± 6.34	18.70 ± 6.37	18.57 ± 5.14
MOD	21.74 ± 7.35	21.38 ± 6.85	20.96 ± 6.45	21.31 ± 6.67	21.25 ± 6.87
NS Proliferation (count)					
HI	1804 ± 3827	3531 ± 2913	1858 ± 1249	4589 ± 4851	3873 ± 5019
MOD	402 ± 215	696 ± 379	459 ± 380	818 ± 271	4151 ± 2550
NS Proliferation (%)					
HI	1.0 ± 1.6	3.1 ± 2.7	1.7 ± 1.1	2.4 ± 2.5	2.3 ± 2.5
MOD	0.3 ± 0.2	0.8 ± 0.6	0.3 ± 0.2	0.5 ± 0.3	2.8 ± 1.8
3+28 Proliferation (count)					
HI	90187 ± 33350	212466 ± 38681	153209 ± 66565	190689 ± 61308	182135 ± 61718
MOD	46238 ± 33894	7989 ± 5713	46817 ± 44791	147718 ± 73024	220317 ± 76041
3+28 Proliferation (%)					
HI	48.1 ± 8.8	73.9 ± 7.7	63.1 ± 15.1	59.3 ± 4.2	63.5 ± 7.5
MOD	21.8 ± 11.5	7.2 ± 4.0	19.9 ± 14.1	54.1 ± 10.0	65.5 ± 9.8
PHA Proliferation (count)					
HI	35459 ± 24861	108723 ± 51420	114966 ± 80636	92524 ± 46200	109777 ± 64221
MOD	5698 ± 3264	5015 ± 4696	20055 ± 16705	24577 ± 25359	13872 ± 6523
PHA Proliferation (%)					
HI	30.5 ± 15.5	59.5 ± 17.9	54.1 ± 16.8	41.7 ± 12.6	50.5 ± 14.0
MOD	4.5 ± 2.9	6.0 ± 4.0	12.5 ± 8.0	15.7 ± 11.4	12.9 ± 5.8
NS CTLA4 (MFI)					
HI	807 ± 634	459 ± 152	665 ± 591	740 ± 510	565 ± 218
MOD	366 ± 155	705 ± 911	480 ± 224	352 ± 43	422 ± 415
3+28 CTLA4 (MFI)					
HI	443 ± 143	483 ± 207	365 ± 62	403 ± 82	445 ± 110
MOD	370 ± 85	289 ± 99	333 ± 105	567 ± 247	422 ± 200
PHA CTLA4 (MFI)					
HI	516 ± 242	575 ± 284	449 ± 181	502 ± 264	483 ± 101
MOD	328 ± 53	392 ± 111	452 ± 209	367 ± 59	414 ± 335

Table 4. Leukocyte and lymphocyte cell counts (Mean ± SD).

	Pre			Post			1hr			4hr			6hr		
Neutrophils (cells/ul)															
HI	2896	±	834	8941	±	3926	11037	±	4046	8945	±	2381	6913	±	1748
MOD	3321	±	549	5609	±	1705	6839	±	2627	7034	±	2503	5738	±	1806
Monocytes (cells/ul)															
HI	435	±	108	544	±	184	643	±	172	578	±	166	784	±	302
MOD	467	±	195	415	±	250	465	±	202	497	±	153	660	±	225
Eosinophils (cells/ul)															
HI	190	±	89	112	±	78	42	±	44	56	±	51	97	±	70
MOD	210	±	206	121	±	133	82	±	96	100	±	121	118	±	138
Basophils (cells/ul)															
HI	32	±	10	33	±	27	24	±	12	26	±	15	34	±	16
MOD	31	±	17	26	±	8	21	±	13	17	±	9	36	±	11
Lymphocytes (cells/ul)															
HI	2159	±	453	1532	±	357	1130	±	296	1670	±	325	1910	±	454
MOD	2659	±	462	1655	±	433	1456	±	354	1903	±	445	2123	±	413

Table 5. Leukocyte and lymphocyte (%) (Mean ± SD).

	Pre			Post			1hr			4hr			6hr		
Neutrophils (%)															
HI	50.2	±	5.5	78.1	±	8.7	84.5	±	5.9	78.6	±	5.4	70.5	±	7.0
MOD	49.8	±	7.7	71.0	±	7.5	75.5	±	8.0	72.2	±	8.4	65.3	±	6.7
Monocytes (%)															
HI	7.9	±	2.1	5.4	±	2.3	5.4	±	2.0	5.2	±	1.5	8.1	±	2.5
MOD	6.9	±	2.3	5.1	±	1.7	5.2	±	1.3	5.3	±	1.3	7.5	±	1.6
Eosinophils (%)															
HI	3.3	±	1.0	1.1	±	0.9	0.4	±	0.5	0.6	±	0.5	1.0	±	0.7
MOD	3.0	±	2.7	1.6	±	1.8	1.1	±	1.3	1.2	±	1.4	1.5	±	1.6
Basophils (%)															
HI	0.6	±	0.2	0.3	±	0.2	0.2	±	0.1	0.2	±	0.1	0.4	±	0.2
MOD	0.5	±	0.3	0.3	±	0.1	0.3	±	0.1	0.2	±	0.1	0.4	±	0.1
Lymphocytes (%)															
HI	38.1	±	4.4	15.1	±	6.1	9.6	±	4.1	15.4	±	4.3	20.1	±	5.4
MOD	39.9	±	6.2	21.9	±	6.8	18.0	±	7.3	21.2	±	7.0	25.3	±	5.8

Table 6. Time in HR Zone (min) (Mean ± SD).

	HI			MOD		
<60%	5.1	±	2.8	34.8	±	17.1
60% -70%	14.3	±	7.4	33.6	±	5.5
70%-80%	17.9	±	4.2	26.5	±	6
80%-90%	25.1	±	7.1	14.8	±	5.7
>90%	35.9	±	14.9	6.4	±	5.1

Table 7. Time in ROG states (min) (Mean ± SD).

	HI			MOD		
Green	25.0	±	9.8	59.9	±	12.5
Orange	12.7	±	5.7	12.8	±	3.4
Red	64.9	±	15.5	28.1	±	10.5

Creatine kinase concentrations (AU).

Subject	Pre	Post	1hr	4hr	6hr
TB02	1239.23	1380.95	1428.74	1611.66	1720.42
TC03	149.96	410.33	388.91	448.23	647.63
TD04	423.51	555.35	845.38	1430.39	1112.34
TE05	182.92	543.81	667.40	978.86	916.24
TH06	710.25	474.60	1644.61	571.82	528.98
TI07	177.97	863.50	517.44	395.50	677.29
TM09	265.31	334.53	405.39	304.86	423.51
TS10	123.59	191.16	268.61	331.23	435.05
CA01	2025.28	1667.68	1555.63	1413.91	1666.04
CB02	163.14	219.17	385.61	660.81	858.56
CC03	937.66	1290.31	1242.52	532.27	1743.49
CD04	388.91	411.98	517.44	1545.74	617.97
CE05	242.24	388.91	481.19	878.34	957.44
CH06	1181.55	477.89	703.66	2162.06	2165.35
CK07	461.41	453.18	716.84	553.70	380.67
CM08	140.07	303.22	484.49	392.20	318.05

HMGB1 Concentrations (ng/ml)

	Pre	Post	1hr	4hr	6hr
TB02	26.47	31.10	30.32	26.77	25.71
TC03	28.30	26.72	24.82	27.50	25.65
TD04	17.55	23.61	17.60	15.97	19.69
TE05	17.83	16.82	17.19	18.43	17.46
TH06	13.14	22.16	20.89	21.29	18.93
TI07	12.39	13.84	16.36	15.01	15.37
TM09	19.97	6.79	8.75	8.32	11.04
TS10	16.84	20.05	19.79	16.33	14.76
CA01	25.07	26.08	25.07	26.38	27.85
CB02	19.87	20.37	23.56	23.06	23.61
CC03	31.88	29.61	27.36	29.93	27.25
CD04	30.14	28.10	27.85	25.03	26.81
CE05	23.68	22.89	22.36	24.47	23.58
CH06	11.01	10.86	11.06	11.32	10.99
CK07	14.01	12.50	12.67	13.05	11.42
CM08	18.29	20.63	17.73	17.27	18.52

IL-1β (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	10.0	9.1	9.1	8.4	8.5
TC03	0.0	0.0	0.0	0.0	0.0
TD04	0.0	0.0	0.0	0.0	0.0
TE05	0.0	0.0	0.0	0.0	0.0
TH06	0.0	0.0	0.0	0.0	0.0
TI07	0.0	0.0	0.0	0.0	0.0
TM09	0.0	0.0	0.0	0.0	0.0
TS10	5.9	6.8	5.2	6.1	6.1
CA01	0.0	0.0	0.0	0.0	0.0
CB02	0.0	0.0	0.0	0.0	0.0
CC03	16.5	20.2	18.1	5.3	16.5
CD04	0.0	0.0	0.0	15.5	0.0
CE05	6.6	7.9	7.8	8.1	9.5
CH06	0.0	0.0	0.0	0.0	0.0
CK07	0.0	0.0	0.0	0.0	0.0
CM08	0.0	0.0	0.0	0.0	0.0

IL-2 (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	20.0	25.1	21.2	19.0	21.9
TC03	0.0	0.0	0.0	0.0	0.0
TD04	0.0	0.0	0.0	0.0	0.0
TE05	0.0	0.0	0.0	0.0	0.0
TH06	0.0	0.0	0.0	0.0	0.0
TI07	0.0	0.0	0.0	0.0	0.0
TM09	0.0	0.0	0.0	0.0	0.0
TS10	7.1	11.8	6.8	7.6	7.2
CA01	0.0	0.0	0.0	0.0	0.0
CB02	0.0	0.0	0.0	0.0	0.0
CC03	19.5	24.4	20.9	5.5	19.7
CD04	0.0	0.0	0.0	19.3	0.0
CE05	9.1	9.7	9.2	9.8	10.2
CH06	0.0	0.0	0.0	0.0	0.0
CK07	0.0	0.0	0.0	0.0	0.0
CM08	0.0	0.0	0.0	0.0	0.0

IL-4 (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	53.5	64.8	71.8	55.9	58.1
TC03	0.0	0.0	0.0	0.0	0.0
TD04	0.0	0.0	0.0	0.0	0.0
TE05	0.0	5.8	8.5	0.0	0.0
TH06	0.0	0.0	0.0	0.0	0.0
TI07	0.0	0.0	0.0	0.0	0.0
TM09	0.0	0.0	0.0	0.0	0.0
TS10	15.7	24.6	15.7	19.3	23.7
CA01	0.0	0.0	0.0	0.0	0.0
CB02	0.0	0.0	0.0	0.0	0.0
CC03	93.4	115.1	101.2	4.7	91.5
CD04	0.0	0.0	0.0	77.2	0.0
CE05	36.1	37.5	43.3	60.7	38.2
CH06	0.0	0.0	0.0	0.0	0.0
CK07	4.5	0.0	0.0	6.0	0.0
CM08	0.0	0.0	0.0	0.0	0.0

IL-6 (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	43.3	57.9	49.3	40.5	50.1
TC03	0.0	0.0	0.0	0.0	0.0
TD04	0.0	0.0	0.0	0.0	0.0
TE05	0.0	10.8	7.4	0.0	0.0
TH06	0.0	0.0	0.0	0.0	0.0
TI07	0.0	0.0	0.0	0.0	0.0
TM09	0.0	19.7	11.4	0.0	0.0
TS10	0.0	13.2	0.0	0.0	0.0
CA01	0.0	0.0	0.0	0.0	0.0
CB02	0.0	11.4	0.0	0.0	0.0
CC03	6.6	8.6	7.6	0.0	8.2
CD04	0.0	0.0	0.0	6.3	0.0
CE05	0.0	0.0	6.4	8.1	0.0
CH06	0.0	0.0	0.0	0.0	0.0
CK07	10.4	6.7	25.0	34.6	20.0
CM08	5.6	0.0	0.0	0.0	0.0

IL-10 (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	37.9	278.5	191.8	39.5	38.6
TC03	0.0	65.1	20.0	0.0	0.0
TD04	0.0	85.7	26.1	0.0	0.0
TE05	12.3	189.0	90.9	15.5	14.9
TH06	0.0	51.7	18.8	0.0	0.0
TI07	0.0	39.3	21.5	0.0	0.0
TM09	0.0	54.6	43.2	0.0	0.0
TS10	20.6	128.8	59.6	22.5	21.8
CA01	0.0	3.8	0.0	0.0	0.0
CB02	0.0	15.2	13.1	0.0	0.0
CC03	48.2	64.9	60.0	0.0	51.5
CD04	0.0	0.0	0.0	45.6	2.0
CE05	19.1	20.1	20.9	14.2	20.2
CH06	0.0	0.0	0.0	0.0	0.0
CK07	5.7	6.7	6.3	12.0	3.6
CM08	75.7	0.0	0.0	225.6	186.5

IL-17a (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	63.3	83.3	89.5	71.2	79.3
TC03	0.0	0.0	0.0	0.0	0.0
TD04	0.0	0.0	0.0	0.0	0.0
TE05	27.5	32.7	24.1	19.2	23.7
TH06	35.8	0.0	0.0	0.0	0.0
TI07	0.0	23.6	20.6	16.6	19.6
TM09	0.0	24.8	28.0	31.4	25.7
TS10	10.9	72.2	15.7	12.6	12.4
CA01	0.0	0.0	0.0	0.0	0.0
CB02	0.0	0.0	0.0	0.0	0.0
CC03	0.0	4.3	0.0	0.0	0.0
CD04	3.3	0.0	0.0	4.3	0.0
CE05	0.0	0.0	0.0	0.0	0.0
CH06	16.6	15.6	3.0	0.0	0.0
CK07	83.6	39.4	147.9	126.3	89.2
CM08	6.0	0.0	0.0	3.2	0.0

INF-γ (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	192.9	262.5	295.9	219.6	288.2
TC03	0.0	0.0	0.0	0.0	0.0
TD04	12.0	12.5	10.7	7.9	11.7
TE05	26.5	35.8	32.0	24.1	28.0
TH06	21.4	7.9	7.9	0.0	0.0
TI07	0.0	9.9	10.7	9.6	10.9
TM09	6.0	13.6	12.5	17.3	9.9
TS10	50.3	226.1	50.0	37.4	35.3
CA01	0.0	0.0	0.0	0.0	0.0
CB02	0.0	0.0	0.0	0.0	0.0
CC03	8.4	8.4	7.6	0.0	0.0
CD04	0.0	0.0	0.0	11.6	0.0
CE05	13.0	13.0	10.2	20.3	15.8
CH06	30.2	21.1	0.0	0.0	0.0
CK07	188.9	90.0	359.0	388.6	204.0
CM08	10.7	0.0	0.0	7.6	0.0

TNF-α (pg/ml)

Subject	Pre	Post	1hr	4hr	6hr
TB02	34.3	56.3	37.4	32.8	29.0
TC03	18.1	29.0	23.5	17.4	16.5
TD04	16.8	19.8	16.5	16.9	18.3
TE05	11.9	23.6	22.2	13.6	12.2
TH06	10.3	20.3	21.9	10.9	11.6
TI07	6.0	8.5	8.7	6.8	6.6
TM09	9.5	13.8	11.6	8.4	7.6
TS10	9.7	18.7	9.3	10.5	7.8
CA01	12.3	12.1	10.8	10.0	8.9
CB02	14.7	23.9	21.9	16.5	17.7
CC03	6.8	6.4	6.9	11.1	6.5
CD04	15.1	11.8	12.7	6.4	15.9
CE05	6.9	6.2	7.6	7.5	6.1
CH06	8.2	7.8	6.8	6.3	6.5
CK07	9.8	9.9	10.5	16.6	13.1
CM08	30.4	6.2	6.5	29.7	26.7

Non Stimulated Proliferation

	Pre	Post	1hr	4hr	6hr
TB02	233	1091	685	2782	1109
TC03	352	2291	2655	5491	3109
TD04	11245	1981	3309	15836	16019
TE05	155	1537	1800	1259	868
TH06	773	9309	704	2500	3036
TI07	283	1333	764	1055	907
TM09	1042	4759	1145	2278	3426
TS10	348	5944	3800	5509	2509
CA01	364	302	222	1000	4963
CB02	717	796	547	887	2585
CC03	500	1333	426	527	6236
CD04	528	436	113	472	9222
CE05	127	1036	1073	1333	3058
CH06	389	891	18	778	1600
CK07	73	491	327	741	2127
CM08	518	283	945	803	3415

Non Stimulated Proliferation (%)

	Pre	Post	1hr	4hr	6hr
TB02	0.2	0.8	0.5	1.7	0.7
TC03	0.6	2.1	2.6	2.8	2.3
TD04	4.8	2	2.3	8.3	8.3
TE05	0.1	1.5	1.5	1.3	0.7
TH06	0.3	6.4	1.5	1.1	1.6
TI07	0.4	0.8	0.7	0.8	0.8
TM09	0.8	3.4	0.8	1.1	2.1
TS10	0.5	7.9	3.7	2.3	2.1
CA01	0.2	0.4	0.1	0.6	3.6
CB02	0.4	1	0.4	1	2
CC03	0.6	2.1	0.6	0.3	5.3
CD04	0.3	0.4	0.1	0.2	5.6
CE05	0.1	0.7	0.4	0.8	1.2
CH06	0.3	1	0.1	0.5	1.1
CK07	0.1	0.5	0.3	0.5	1.3
CM08	0.2	0.6	0.5	0.4	2.4

3+28 Stimulated Proliferation

	Pre	Post	1hr	4hr	6hr
TB02	68421	149661	188571	171273	144855
TC03	60730	165200	238964	227554	189018
TD04	108870	221382	123315	120357	117667
TE05	58236	203527	91056	86981	136418
TH06	145509	235696	168259	265982	215182
TI07	56902	250545	37073	192327	179673
TM09	112890	215000	163254	234291	160214
TS10	109939	258719	215182	226745	314052
CA01	85268	13717	112482	239393	293407
CB02	89245	18491	43315	68709	142418
CC03	12566	6075	5635	134500	261019
CD04	26212	2727	17925	127296	91811
CE05	23891	9564	96722	116182	241509
CH06	45418	5667	252	94352	168945
CK07	7455	6245	13611	121148	293268
CM08	79851	1423	84596	280160	270160

3+28 Stimulated Proliferation (%)

	Pre	Post	1hr	4hr	6hr
TB02	31.4	60.2	67.3	57.4	58.2
TC03	51	77.6	79.6	65.4	73.1
TD04	48.9	80.8	55.9	58.9	56.9
TE05	45.8	77.3	49	50.8	57.8
TH06	49.4	73.7	80.2	62	62
TI07	41.9	69.4	40.6	60.2	63.8
TM09	58.8	67.9	55.2	59.8	59.6
TS10	57.8	84	76.8	59.5	76.8
CA01	37.7	12.2	40.6	68.9	72.7
CB02	34	13.8	23.4	47.7	58.1
CC03	11.8	5.6	6.1	46.8	74.3
CD04	14.3	3	11.9	50	47.4
CE05	10.8	6.3	30	44.6	60.2
CH06	26	8.3	2.3	50.2	64.1
CK07	9.1	5.3	10.7	54.4	73.2
CM08	30.4	3	33.9	70.3	74

PHA Stimulated Proliferation

	Pre	Post	1hr	4hr	6hr
TB02	8463	84759	75815	93036	52241
TC03	51532	127519	185038	152870	181345
TD04	65618	138148	115370	99778	85418
TE05	6600	32241	94925	45741	40873
TH06	61027	169982	38407	59527	84302
TI07	19232	61630	44385	116982	223691
TM09	54036	82090	86462	25759	78444
TS10	17165	173418	279327	146500	131905
CA01	8018	2278	9500	6481	7660
CB02	10148	8407	20255	5527	5151
CC03	1472	3315	1036	4982	7722
CD04	8782	15321	18648	66741	18904
CE05	2148	4000	38093	13660	14604
CH06	2717	1815	155	6429	21774
CK07	6407	3558	25788	57547	21423
CM08	5890	1425	46963	35250	13735

PHA Stimulated Proliferation (%)

	Pre	Post	1hr	4hr	6hr
TB02	15	49.5	40.4	44.5	33.2
TC03	58.9	77.1	74.9	53.1	70.6
TD04	33.5	66	55	46.4	46.3
TE05	9.7	47.5	53.4	38.9	38.1
TH06	36.1	78.6	58.6	36.2	47.9
TI07	25.3	33.4	29.4	53	69.8
TM09	40.4	44.8	42.3	14.4	41.2
TS10	25.3	78.9	78.4	47.4	56.6
CA01	5.4	3.5	6.2	5.9	8
CB02	7.6	12.1	17	10.3	6.1
CC03	1.8	5.1	1.9	3.9	10.6
CD04	5.9	12.7	14.5	27.3	12.4
CE05	1.2	3.1	15.1	10.3	9.1
CH06	2.1	4.7	2.7	8.9	22.8
CK07	9.2	3.6	19.1	34.5	19.7
CM08	3.1	3.3	23.7	24.7	14.1

CTLA4 MFI (non stim)

	Pre	Post	1hr	4hr	6hr
TB02	274	496	470	358	370
TC03	1520	664	839	763	665
TD04	768	343	380	1091	485
TE05	143	343	377	374	524
TH06	470	500	585	1845	458
TI07	338	366	251	459	1054
TM09	1050	281	359	419	562
TS10	1896	681	2058	612	400
CA01	262	313	884	281	1446
CB02	327	341	297	323	236
CC03	258	578	268	379	232
CD04	268	374	658	386	260
CE05	673	336	458	337	271
CH06	268	2946	636	415	297
CK07	338	289	289	372	332
CM08	537	459	348	323	302

CTLA4 MFI (3+28)

	Pre	Post	1hr	4hr	6hr
TB02	277	418	441	375	271
TC03	723	971	314	545	451
TD04	347	360	343	334	566
TE05	321	541	353	354	568
TH06	541	427	392	428	553
TI07	404	442	282	365	405
TM09	470	373	334	321	387
TS10	462	332	461	501	358
CA01	470	519	516	347	429
CB02	465	212	283	335	266
CC03	426	257	298	394	343
CD04	304	251	283	379	787
CE05	370	230	458	723	264
CH06	234	325	189	542	260
CK07	300	277	333	883	667
CM08	387	239	303	932	358

CTLA4 MFI (PHA)

	Pre	Post	1hr	4hr	6hr
TB02	337	480	415	397	412
TC03	1005	1226	339	504	663
TD04	378	619	351	1142	508
TE05	275	410	702	396	483
TH06	437	607	770	437	352
TI07	485	332	383	432	384
TM09	746	374	305	329	496
TS10	467	549	329	379	564
CA01	379	400	366	354	1236
CB02	317	401	592	344	324
CC03	343	280	353	376	293
CD04	270	374	305	300	354
CE05	402	587	402	295	248
CH06	284	504	308	417	225
CK07	368	342	917	374	332
CM08	264	251	371	474	300

Neutrophils (cells/ul)

	Pre	Post	1hr	4hr	6hr
TB02	3009	16800	18655	13594	9862
TC03	2734	7807	10811	8894	7003
TD04	2801	7722	10816	9013	7347
TE05	2295	8195	8615	8080	5285
TH06	3231	9587	12859	10020	7646
TI07	4610	11633	13498	9607	8173
TM09	2776	5971	6973	6634	5418
TS10	1714	3813	6068	5721	4572
CA01	3008	4602	5752	6240	5283
CB02	2759	5677	11779	11578	9074
CC03	3657	6871	7185	6565	5290
CD04	3049	2911	3355	4004	3380
CE05	3558	5964	6771	6354	5168
CH06	2618	4820	5290	6184	5600
CK07	4230	5313	5332	5306	4444
CM08	3686	8712	9245	10037	7667

Monocytes (cells/ul)

	Pre	Post	1hr	4hr	6hr
TB02	424	582	800	543	835
TC03	423	628	743	523	670
TD04	626	804	793	812	1434
TE05	377	562	717	636	635
TH06	511	479	562	787	864
TI07	273	223	289	339	429
TM09	490	699	694	576	828
TS10	357	376	547	408	576
CA01	443	304	357	499	558
CB02	397	281	603	375	743
CC03	540	300	368	599	722
CD04	332	206	264	312	308
CE05	402	470	460	442	655
CH06	363	340	306	448	538
CK07	339	421	469	488	656
CM08	920	998	889	812	1100

Eosinophils (cells/ul)

	Pre	Post	1hr	4hr	6hr
TB02	132	116	0	0	12
TC03	163	144	50	44	65
TD04	87	29	13	23	45
TE05	170	83	20	40	73
TH06	291	57	29	38	97
TI07	359	79	46	97	198
TM09	165	285	143	163	207
TS10	156	103	31	46	79
CA01	698	437	291	355	432
CB02	155	53	27	0	12
CC03	135	73	37	67	87
CD04	241	147	154	176	171
CE05	174	101	74	141	128
CH06	61	25	20	8	16
CK07	58	41	21	44	41
CM08	160	93	34	12	55

Basophils (cells/ul)

	Pre	Post	1hr	4hr	6hr
TB02	44	78	41	0	12
TC03	31	41	13	11	28
TD04	17	39	39	35	45
TE05	41	52	20	40	22
TH06	36	0	14	38	32
TI07	39	0	30	36	44
TM09	29	37	29	29	63
TS10	21	17	8	15	22
CA01	30	31	17	19	45
CB02	56	23	40	0	47
CC03	21	18	18	29	44
CD04	20	10	11	13	17
CE05	13	34	28	19	34
CH06	28	25	20	25	31
CK07	58	28	36	15	28
CM08	23	35	0	12	44

Lymphocytes (cells/ul)

	Pre	Post	1hr	4hr	6hr
TB02	1892	1824	1005	1364	1379
TC03	1749	1679	983	1428	1535
TD04	2268	1205	1339	1717	2330
TE05	1716	1508	727	1303	1285
TH06	3032	1277	936	1816	2160
TI07	2519	1166	1338	2021	2156
TM09	2240	2208	1663	2198	2484
TS10	1853	1391	1047	1509	1951
CA01	3323	2426	1884	2486	2682
CB02	2833	1566	951	1447	1923
CC03	2748	1838	1592	2242	2558
CD04	2860	1627	1716	1996	1824
CE05	2553	1831	1868	2444	2516
CH06	2431	1090	1163	1635	1615
CK07	1715	1097	1243	1547	1732
CM08	2812	1763	1231	1427	2134

Neutrophils (%)

	Pre	Post	1hr	4hr	6hr
TB02	54.7	86.6	91.0	87.7	81.5
TC03	53.6	75.8	85.8	81.6	75.3
TD04	48.3	78.8	83.2	77.7	65.6
TE05	49.9	78.8	85.3	80.0	72.4
TH06	45.5	84.1	89.3	78.9	70.8
TI07	59.1	88.8	88.8	79.4	74.3
TM09	48.7	64.9	73.4	69.1	60.2
TS10	41.8	66.9	78.8	74.3	63.5
CA01	40.1	59.0	69.3	65.0	58.7
CB02	44.5	74.7	87.9	86.4	76.9
CC03	51.5	75.5	78.1	69.1	60.8
CD04	46.9	59.4	61.0	61.6	59.3
CE05	53.1	71.0	73.6	67.6	60.8
CH06	47.6	76.5	77.8	74.5	71.8
CK07	66.1	77.0	75.1	71.7	64.4
CM08	48.5	75.1	81.1	81.6	69.7

Monocytes (%)

	Pre	Post	1hr	4hr	6hr
TB02	7.7	3.0	3.9	3.5	6.9
TC03	8.3	6.1	5.9	4.8	7.2
TD04	10.8	8.2	6.1	7.0	12.8
TE05	8.2	5.4	7.1	6.3	8.7
TH06	7.2	4.2	3.9	6.2	8.0
TI07	3.5	1.7	1.9	2.8	3.9
TM09	8.6	7.6	7.3	6.0	9.2
TS10	8.7	6.6	7.1	5.3	8.0
CA01	5.9	3.9	4.3	5.2	6.2
CB02	6.4	3.7	4.5	2.8	6.3
CC03	7.6	3.3	4.0	6.3	8.3
CD04	5.1	4.2	4.8	4.8	5.4
CE05	6.0	5.6	5.0	4.7	7.7
CH06	6.6	5.4	4.5	5.4	6.9
CK07	5.3	6.1	6.6	6.6	9.5
CM08	12.1	8.6	7.8	6.6	10.0

Eosinophils (%)

	Pre	Post	1hr	4hr	6hr
TB02	2.4	.6	.0	.0	.1
TC03	3.2	1.4	.4	.4	.7
TD04	1.5	.3	.1	.2	.4
TE05	3.7	.8	.2	.4	1.0
TH06	4.1	.5	.2	.3	.9
TI07	4.6	.6	.3	.8	1.8
TM09	2.9	3.1	1.5	1.7	2.3
TS10	3.8	1.8	.4	.6	1.1
CA01	9.3	5.6	3.5	3.7	4.8
CB02	2.5	.7	.2	.0	.1
CC03	1.9	.8	.4	.7	1.0
CD04	3.7	3.0	2.8	2.7	3.0
CE05	2.6	1.2	.8	1.5	1.5
CH06	1.1	.4	.3	.1	.2
CK07	.9	.6	.3	.6	.6
CM08	2.1	.8	.3	.1	.5

Basophils (%)

	Pre	Post	1hr	4hr	6hr
TB02	.8	.4	.2	.0	.1
TC03	.6	.4	.1	.1	.3
TD04	.3	.4	.3	.3	.4
TE05	.9	.5	.2	.4	.3
TH06	.5	.0	.1	.3	.3
TI07	.5	.0	.2	.3	.4
TM09	.5	.4	.3	.3	.7
TS10	.5	.3	.1	.2	.3
CA01	.4	.4	.2	.2	.5
CB02	.9	.3	.3	.0	.4
CC03	.3	.2	.2	.3	.5
CD04	.3	.2	.2	.2	.3
CE05	.2	.4	.3	.2	.4
CH06	.5	.4	.3	.3	.4
CK07	.9	.4	.5	.2	.4
CM08	.3	.3	.0	.1	.4

Lymphocytes (%)

	Pre	Post	1hr	4hr	6hr
TB02	34.4	9.4	4.9	8.8	11.4
TC03	34.3	16.3	7.8	13.1	16.5
TD04	39.1	12.3	10.3	14.8	20.8
TE05	37.3	14.5	7.2	12.9	17.6
TH06	42.7	11.2	6.5	14.3	20.0
TI07	32.3	8.9	8.8	16.7	19.6
TM09	39.3	24.0	17.5	22.9	27.6
TS10	45.2	24.4	13.6	19.6	27.1
CA01	44.3	31.1	22.7	25.9	29.8
CB02	45.7	20.6	7.1	10.8	16.3
CC03	38.7	20.2	17.3	23.6	29.4
CD04	44.0	33.2	31.2	30.7	32.0
CE05	38.1	21.8	20.3	26.0	29.6
CH06	44.2	17.3	17.1	19.7	20.7
CK07	26.8	15.9	17.5	20.9	25.1
CM08	37.0	15.2	10.8	11.6	19.4

Time (min) in Heart Rate Zones

Subject	Average	<60% MHR	60-70% MHR	70-80% MHR	80-90% MHR	>90% MHR
TB02	164	2.9	6.9	26.9	18.5	43.7
TC03	154	7.8	11.3	19.2	25.9	34.8
TD04	170	4.9	1.3	13.9	21.5	58.9
TE05	160	4.1	13.3	18.4	20.9	41.3
TH06	149	7.8	24.9	13.1	38.4	9.0
TI07	151	9.5	23.3	14.7	29.5	19.9
TM09	162	2.4	15.5	16.6	15.3	48.1
TS10	156	1.2	17.7	20.2	30.6	31.4
CA01	143	14.7	37.1	34.8	14.9	14.1
CB02	132	30.9	40.6	32.6	7.7	5.4
CC03	142	19.1	32.2	25.8	25.2	13.7
CD04	119	58.3	27.2	22.7	8.7	0.5
CE05	137	19.5	42.2	27.5	16.8	9.1
CH06	131	34.9	33.6	25.6	20.1	2.6
CK07	115	64.5	28.5	14.0	9.2	0.1
CM08	123	36.2	27.6	29.4	16.0	5.6

	Temperature (˚C)	
	Avg	Peak
TB02	38.8	39.5
TC03	38.2	38.8
TD04	39.2	40.0
TE05	38.6	39.4
TH06	38.2	38.7
TI07	38.3	39.1
TM09	38.7	39.6
TS10	38.5	38.9
CA01	38.1	39.2
CB02	37.9	38.1
CC03	38.1	38.7
CD04	37.8	38.0
CE05	38.0	38.5
CH06	37.9	38.4
CK07	37.7	38.0
CM08	37.5	38.5

Appendix C: Immunoendocrine Responses to Marine Corps Martial Arts Training

Table 1. Serial measures for endocrine responses to MCMAP training across visits.

	Visit 1			Visit 2			Visit 3		
Cortisol (mcg/dl)									
Baseline	16.92	±	3.37	16.70	±	3.25	16.48	±	3.60
AUC	1067.83	±	269.47	1030.42	±	264.80	1053.02	±	250.77
Peak Concentration	20.47	±	4.70	20.09	±	4.63	20.58	±	4.08
Time to Peak (min)	16.67	±	19.57	8.33	±	10.42	12.50	±	11.62
Epinephrine (pcg/ml)									
Baseline	27.22	±	28.74	38.11	±	72.38	21.58	±	20.88
AUC	2267.50	±	1623.18	2579.17	±	2255.13	2218.54	±	1860.68
Peak Concentration	81.39	±	50.70	93.06	±	78.36	80.67	±	63.89
Time to Peak (min)	7.08	±	10.45	5.00	±	11.34	7.50	±	10.45
Norepinephrine (pcg/ml)									
Baseline	412.92	±	171.54	432.75	±	173.96	396.67	±	139.81
AUC	35330.42	±	12633.12	34236.25	±	10293.48	37547.92	±	14682.61
Peak Concentration	969.44	±	476.39	987.64	±	367.47	1134.31	±	636.17
Time to Peak (min)	11.67	±	19.01	8.75	±	16.96	13.33	±	19.24

Table 2. Serial measures for immunoglobulin-G and -M responses to MCMAP training across visits.

	Visit 1			Visit 2			Visit 3		
IgG (mg/dl)									
Baseline	1110.78	±	211.69	1084.08	±	213.98	1084.47	±	212.28
AUC	65958.54	±	12437.23	64556.46	±	13601.66	64285.42	±	12704.73
Peak Concentration	1172.25	±	220.58	1176.69	±	244.07	1168.19	±	234.02
Time to Peak (min)	15.00	±	20.60	5.00	±	8.02	11.67	±	19.01
IgM (mg/dl)									
Baseline	117.06	±	49.01	113.06	±	47.93	112.81	±	46.24
AUC	6836.46	±	2843.50	6567.92	±	2882.61	6619.79	±	2765.66
Peak Concentration	122.00	±	50.53	119.36	±	51.66	119.28	±	47.47
Time to Peak (min)	15.83	±	20.27	3.75	±	10.98	10.42	±	17.50

Table 3. Serial measures for neutrophil oxidative burst (%) following MCMAP training.

	Visit 1			Visit 2			Visit 3		
Neutrophil Oxidative Burst (%)									
Baseline	95.53	±	4.14	92.64	±	6.02	92.67	±	16.33
AUC	5716.04	±	399.58	5469.58	±	594.25	5703.54	±	311.78
Peak Concentration	98.22	±	2.17	96.56	±	3.52	97.72	±	1.85
Time to Peak (min)	24.17	±	20.37	25.83	±	24.48	23.33	±	20.11

Table 4. Serial measures for lymphocyte responses (%) to MCMAP training across visits.

	Visit 1			Visit 2			Visit 3		
CD3+ (%)									
Baseline	68.42	±	13.79	71.64	±	6.19	70.39	±	13.73
AUC	4223.54	±	446.92	4254.38	±	401.72	4261.25	±	443.49
Peak Concentration	74.86	±	5.61	75.14	±	5.61	75.22	±	5.36
Time to Peak (min)	36.67	±	16.60	28.75	±	14.06	31.25	±	19.43
CD4+ (%)									
Baseline	40.28	±	8.91	42.03	±	5.78	42.31	±	8.91
AUC	2509.79	±	341.59	2528.96	±	300.23	2533.33	±	301.49
Peak Concentration	46.72	±	4.80	46.75	±	4.82	47.19	±	4.13
Time to Peak (min)	40.42	±	15.96	35.83	±	14.90	39.17	±	18.03
CD8+ (%)									
Baseline	26.06	±	7.25	27.83	±	6.12	26.42	±	7.50
AUC	1612.92	±	351.89	1631.88	±	381.96	1635.21	±	372.98
Peak Concentration	29.53	±	6.95	30.17	±	7.15	29.83	±	7.15
Time to Peak (min)	15.00	±	17.20	11.67	±	12.98	16.67	±	18.21
CD19+ (%)									
Baseline	15.33	±	5.31	15.86	±	5.20	15.44	±	6.03
AUC	886.25	±	231.26	917.50	±	248.28	883.75	±	236.53
Peak Concentration	17.08	±	4.27	17.69	±	4.55	17.08	±	4.66
Time to Peak (min)	38.75	±	20.71	32.92	±	18.57	33.75	±	21.02
Natural Killer Cells (%)									
Baseline	12.22	±	8.11	11.08	±	6.59	10.06	±	5.69
AUC	721.88	±	351.28	689.79	±	314.21	732.29	±	335.58
Peak Concentration	22.72	±	10.05	23.47	±	9.85	23.44	±	11.00
Time to Peak (min)	6.25	±	11.55	3.33	±	6.32	7.92	±	14.56

Table 5. Serial measures for lymphocyte responses (cells/ul) to MCMAP training across visits.

	Visit 1			Visit 2			Visit 3		
CD3+ (cells/ul)									
Baseline	1438.81	±	456.38	1481.50	±	360.87	1409.06	±	380.54
AUC	65745.42	±	19290.44	69032.71	±	20269.22	69660.00	±	15933.50
Peak Concentration	1631.89	±	487.05	1739.33	±	526.03	1698.75	±	549.96
Time to Peak (min)	4.17	±	11.12	1.67	±	4.78	5.83	±	11.50
CD4+ (cells/ul)									
Baseline	839.86	±	264.25	878.42	±	214.37	848.67	±	230.37
AUC	37898.33	±	8829.30	40036.04	±	11062.64	40391.25	±	7829.87
Peak Concentration	859.22	±	212.75	914.00	±	249.63	891.86	±	204.53
Time to Peak (min)	4.17	±	14.17	1.67	±	5.98	7.92	±	14.56
CD8+ (cells/ul)									
Baseline	552.28	±	227.73	590.50	±	212.30	537.39	±	188.79
AUC	26176.88	±	11384.15	27523.96	±	11238.26	28061.04	±	10101.08
Peak Concentration	733.83	±	333.26	800.06	±	348.70	796.03	±	387.01
Time to Peak (min)	4.17	±	11.12	0.83	±	3.48	5.83	±	8.24
CD19+ (cells/ul)									
Baseline	321.97	±	119.85	320.53	±	115.71	305.61	±	128.75
AUC	13370.63	±	3980.73	14322.29	±	4714.66	13908.75	±	4140.88
Peak Concentration	311.53	±	104.92	328.64	±	127.96	313.00	±	110.85
Time to Peak (min)	7.50	±	15.83	4.58	±	11.79	11.25	±	18.76
Natural Killer Cells (cell/ul)									
Baseline	258.78	±	174.16	230.94	±	159.59	199.39	±	122.04
AUC	12962.50	±	7668.89	12731.25	±	6659.08	14675.00	±	9727.81
Peak Concentration	584.03	±	358.36	639.39	±	368.77	697.00	±	517.60
Time to Peak (min)	5.42	±	11.43	3.33	±	6.32	6.25	±	11.55

Table 6. Serial measures for leukocyte responses (cells/ul) to MCMAP training across visits.

	Visit 1	Visit 2	Visit 3
Neutrophils (cells/ul)			
Baseline	3644.66 ± 1537.47	3242.31 ± 766.54	3427.64 ± 1640.72
AUC	334311.88 ± 128037.17	270107.29 ± 89973.89	285113.75 ± 128120.83
Peak Concentration	7169.25 ± 2648.65	5954.89 ± 1949.04	6080.78 ± 2814.09
Time to Peak (min)	35.42 ± 27.58	30.83 ± 28.45	30.00 ± 28.23
Monocytes (cells/ul)			
Baseline	516.64 ± 223.79	475.72 ± 145.72	486.31 ± 223.06
AUC	28935.83 ± 10851.07	27727.29 ± 9626.07	30366.46 ± 13812.81
Peak Concentration	662.61 ± 260.73	642.39 ± 254.33	707.50 ± 379.66
Time to Peak (min)	17.50 ± 23.92	7.50 ± 17.38	18.75 ± 21.92
Eosinophils (cells/ul)			
Baseline	207.17 ± 198.31	215.81 ± 210.40	197.42 ± 178.04
AUC	9019.79 ± 9324.69	9397.08 ± 10767.42	8361.67 ± 7270.19
Peak Concentration	218.17 ± 211.90	232.42 ± 244.00	203.67 ± 175.83
Time to Peak (min)	6.67 ± 12.65	3.75 ± 10.98	9.17 ± 13.07
Basophils (cells/ul)			
Baseline	27.19 ± 13.10	24.94 ± 13.97	28.39 ± 11.60
AUC	1634.38 ± 687.48	1611.46 ± 702.87	1793.54 ± 630.24
Peak Concentration	42.75 ± 19.00	41.33 ± 18.35	44.31 ± 14.68
Time to Peak (min)	14.58 ± 19.80	21.67 ± 21.35	25.42 ± 21.46

Table 7. Serial measures for leukocyte responses (%) to MCMAP training across visits.

	Visit 1	Visit 2	Visit 3
Neutrophils (%)			
Baseline	52.52 ± 14.10	53.30 ± 6.55	53.03 ± 12.95
AUC	4087.83 ± 687.75	3842.71 ± 562.65	3876.23 ± 552.39
Peak Concentration	76.06 ± 9.11	72.98 ± 8.73	72.42 ± 9.23
Time to Peak (min)	48.33 ± 21.25	40.42 ± 24.53	42.92 ± 24.62
Monocytes (%)			
Baseline	7.99 ± 3.09	7.86 ± 1.72	7.68 ± 2.42
AUC	367.35 ± 106.61	409.00 ± 133.46	431.81 ± 116.28
Peak Concentration	7.55 ± 1.80	8.23 ± 2.24	8.54 ± 2.12
Time to Peak (min)	11.67 ± 19.01	10.42 ± 17.13	12.50 ± 17.75
Eosinophils (%)			
Baseline	3.21 ± 2.94	3.47 ± 3.15	3.32 ± 3.41
AUC	117.54 ± 131.17	136.04 ± 146.34	131.88 ± 148.58
Peak Concentration	2.70 ± 2.82	3.02 ± 2.98	2.86 ± 2.90
Time to Peak (min)	10.42 ± 13.80	6.67 ± 9.78	8.33 ± 13.63
Basophils (%)			
Baseline	0.43 ± 0.20	0.41 ± 0.21	0.43 ± 0.28
AUC	21.60 ± 8.31	23.83 ± 9.63	27.23 ± 10.48
Peak Concentration	0.55 ± 0.18	0.58 ± 0.22	0.64 ± 0.20
Time to Peak (min)	16.25 ± 18.06	20.83 ± 20.99	26.25 ± 21.02

Table 8. Effect of Marine Corps Martial Arts Training on endocrine parameters. Values are Mean ± SD.

Visit	Time	Cortisol (mcg/dl)	Epinephrine (pcg/ml)	Norepinephrine (pcg/ml)
1	Post	19.00 ± 4.37	73.83 ± 43.18	917.50 ± 489.32
	R15	18.68 ± 4.67	50.86 ± 46.64	519.00 ± 244.38
	R30	17.69 ± 4.98	29.89 ± 36.43	583.75 ± 355.94
	R45	16.79 ± 5.02	17.44 ± 24.29	517.78 ± 179.55
	R60	15.93 ± 4.74	20.75 ± 25.20	584.69 ± 180.65
2	Post	18.97 ± 5.02	85.50 ± 57.45	966.47 ± 388.49
	R15	18.76 ± 4.78	41.06 ± 37.90	496.81 ± 167.17
	R30	17.30 ± 4.60	27.86 ± 36.64	505.89 ± 179.37
	R45	16.03 ± 4.44	26.39 ± 28.20	517.44 ± 163.20
	R60	14.28 ± 3.82	31.06 ± 37.85	534.31 ± 165.51
3	Post	19.62 ± 4.57	77.36 ± 63.96	1101.25 ± 674.88
	R15	19.19 ± 4.24	45.97 ± 41.22	571.36 ± 261.51
	R30	17.32 ± 4.12	23.83 ± 22.37	556.94 ± 247.36
	R45	16.41 ± 4.21	22.97 ± 25.16	516.92 ± 238.38
	R60	15.05 ± 4.28	18.53 ± 20.01	551.89 ± 236.17

Table 9. Effect of Marine Corps Martial Arts Training on immunoglobulins-G & -M. Values are presented as mg/dl (Mean ± SD).

Visit	Time	IgG			IgM		
1	Post	1153.92	±	209.22	120.11	±	49.57
	R15	1086.78	±	194.56	112.81	±	46.74
	R30	1074.50	±	207.25	111.31	±	47.08
	R45	1093.83	±	232.83	113.56	±	48.64
	R60	1092.92	±	205.79	113.14	±	46.35
2	Post	1167.42	±	235.71	118.69	±	51.37
	R15	1077.97	±	215.60	109.08	±	47.71
	R30	1066.47	±	223.40	107.28	±	46.10
	R45	1055.28	±	214.22	107.81	±	47.55
	R60	1065.92	±	216.79	109.22	±	46.89
3	Post	1158.75	±	229.52	118.08	±	47.30
	R15	1080.03	±	222.54	111.11	±	45.51
	R30	1058.17	±	218.65	108.36	±	45.51
	R45	1056.83	±	218.42	108.92	±	46.15
	R60	1067.97	±	215.71	109.64	±	45.72

Table 10. Effect of Marine Corps Martial Arts Training on lymphocyte subsets. Values are presented as percent (%) (Mean ± SD).

Visit	Time	CD3	CD4	CD8	CD19	NKC
1	Post	64.25 ± 10.22	33.83 ± 7.55	28.33 ± 7.50	11.64 ± 3.42	22.42 ± 10.45
	R15	72.08 ± 7.08	42.44 ± 6.74	27.78 ± 6.07	14.89 ± 4.46	11.75 ± 6.71
	R30	74.06 ± 5.60	45.64 ± 5.22	27.00 ± 5.31	15.83 ± 4.23	8.44 ± 4.33
	R45	73.28 ± 6.02	45.47 ± 4.93	26.31 ± 5.34	16.36 ± 4.24	9.14 ± 4.95
	R60	72.58 ± 6.54	44.81 ± 4.65	26.28 ± 5.36	15.86 ± 3.80	10.14 ± 5.47
2	Post	63.78 ± 9.78	33.58 ± 6.72	28.44 ± 7.74	11.61 ± 3.64	23.25 ± 9.98
	R15	72.86 ± 6.41	43.11 ± 5.82	28.22 ± 6.50	15.42 ± 3.93	10.44 ± 5.86
	R30	74.11 ± 5.59	45.47 ± 5.35	27.14 ± 6.01	16.69 ± 4.27	8.14 ± 4.34
	R45	73.44 ± 5.76	45.36 ± 4.62	26.58 ± 5.68	16.67 ± 4.81	8.53 ± 4.21
	R60	71.97 ± 7.00	44.56 ± 5.11	26.11 ± 5.84	16.53 ± 4.46	10.11 ± 5.88
3	Post	64.28 ± 11.01	33.89 ± 7.72	28.83 ± 7.83	11.31 ± 3.13	22.94 ± 11.35
	R15	71.03 ± 7.41	41.42 ± 5.56	27.83 ± 6.18	14.33 ± 3.55	13.11 ± 6.80
	R30	73.86 ± 5.43	45.50 ± 4.84	26.69 ± 5.47	15.92 ± 4.33	8.78 ± 4.09
	R45	74.19 ± 5.48	46.31 ± 4.17	26.58 ± 5.53	16.17 ± 4.69	8.53 ± 3.64
	R60	72.86 ± 5.63	45.31 ± 4.23	26.14 ± 5.37	16.53 ± 4.67	9.33 ± 4.11

Table 11. Effect of Marine Corps Martial Arts Training on lymphocyte subsets. Values are presented as cells/ul (Mean ± SD).

Visit	Time	CD3	CD4	CD8	CD19	NKC
1	Post	1551.08 ± 487.87	794.36 ± 174.15	707.69 ± 344.04	276.06 ± 86.63	577.28 ± 365.77
	R15	1065.44 ± 304.75	615.39 ± 146.23	420.75 ± 184.08	213.86 ± 68.74	180.19 ± 142.68
	R30	977.86 ± 247.88	594.83 ± 140.48	359.28 ± 133.08	208.81 ± 65.93	111.97 ± 56.05
	R45	925.33 ± 275.43	571.67 ± 157.20	337.08 ± 130.06	201.61 ± 64.89	113.19 ± 67.42
	R60	972.25 ± 292.11	590.14 ± 165.27	357.31 ± 134.59	208.75 ± 62.88	132.58 ± 78.39
2	Post	1660.97 ± 558.59	862.89 ± 261.90	766.47 ± 358.94	291.83 ± 116.24	630.78 ± 374.99
	R15	1122.86 ± 338.19	652.64 ± 188.22	442.11 ± 186.00	232.53 ± 73.40	161.58 ± 108.31
	R30	1039.97 ± 313.58	628.53 ± 175.00	385.33 ± 159.20	230.94 ± 79.81	110.56 ± 65.54
	R45	1003.97 ± 301.02	618.11 ± 181.83	369.42 ± 145.14	220.58 ± 75.37	111.67 ± 63.24
	R60	984.47 ± 284.21	610.33 ± 172.05	364.39 ± 145.44	223.42 ± 77.94	131.39 ± 77.12
3	Post	1704.19 ± 537.31	879.72 ± 195.90	798.06 ± 384.22	297.97 ± 110.69	694.50 ± 520.03
	R15	1114.28 ± 227.07	648.83 ± 119.00	444.64 ± 141.56	222.69 ± 68.08	207.67 ± 131.02
	R30	1008.36 ± 218.91	620.08 ± 132.87	372.08 ± 124.62	214.81 ± 65.45	119.72 ± 63.72
	R45	981.25 ± 214.77	609.42 ± 122.58	354.39 ± 111.61	212.00 ± 68.06	114.36 ± 61.81
	R60	958.64 ± 236.58	596.78 ± 141.05	348.08 ± 116.06	211.94 ± 64.45	122.06 ± 61.38

Table 12. Effect of Marine Corps Martial Arts Training on leukocytes. Values are presented as percent (%) (Mean ± SD).

Visit	Time	Neutrophils	Monocytes	Eosinophils	Basophils
1	Post	61.25 ± 9.97	6.99 ± 1.71	2.32 ± 2.41	0.41 ± 0.21
	R15	68.78 ± 9.84	6.42 ± 1.73	2.21 ± 2.31	0.40 ± 0.19
	R30	70.76 ± 10.91	6.38 ± 2.07	2.02 ± 2.11	0.39 ± 0.18
	R45	74.68 ± 9.43	5.78 ± 1.70	1.64 ± 1.88	0.33 ± 0.20
	R60	75.46 ± 9.53	5.89 ± 1.85	1.46 ± 1.79	0.29 ± 0.21
2	Post	56.17 ± 7.93	7.54 ± 2.40	2.62 ± 2.65	0.43 ± 0.23
	R15	64.47 ± 8.71	7.16 ± 2.46	2.54 ± 2.85	0.40 ± 0.20
	R30	68.47 ± 9.23	6.73 ± 2.40	2.22 ± 2.62	0.42 ± 0.22
	R45	70.48 ± 9.45	6.58 ± 2.37	1.91 ± 2.07	0.36 ± 0.21
	R60	72.40 ± 9.07	6.74 ± 2.42	1.62 ± 1.55	0.32 ± 0.20
3	Post	55.29 ± 10.89	8.20 ± 2.25	2.42 ± 2.39	0.46 ± 0.21
	R15	63.15 ± 10.41	7.35 ± 2.14	2.48 ± 2.77	0.50 ± 0.22
	R30	68.24 ± 9.79	6.89 ± 1.95	2.16 ± 2.45	0.43 ± 0.24
	R45	69.90 ± 10.51	6.88 ± 1.97	1.89 ± 2.53	0.45 ± 0.24
	R60	72.16 ± 9.36	6.79 ± 2.11	1.67 ± 1.93	0.43 ± 0.21

Table 13. Effect of Marine Corps Martial Arts Training on leukocytes. Values are presented as cells/ul (Mean ± SD).

Visit	Time	Neutrophils	Monocytes	Eosinophils	Basophils
1	Post	5503.06 ± 2149.86	621.08 ± 250.14	200.19 ± 196.30	35.92 ± 21.16
	R15	5061.81 ± 1930.38	457.03 ± 162.50	153.72 ± 149.66	27.06 ± 12.99
	R30	5417.11 ± 2214.46	456.36 ± 189.86	145.22 ± 146.24	26.25 ± 12.58
	R45	6269.42 ± 2400.06	463.36 ± 189.15	129.14 ± 140.19	25.72 ± 19.35
	R60	6862.31 ± 2700.40	503.50 ± 199.59	119.83 ± 133.19	22.61 ± 15.69
2	Post	4512.28 ± 1317.67	610.81 ± 271.63	217.75 ± 244.36	33.83 ± 20.29
	R15	4075.39 ± 1421.02	439.58 ± 170.61	160.50 ± 197.44	24.31 ± 11.81
	R30	4670.39 ± 1683.50	440.00 ± 181.97	144.06 ± 172.36	27.75 ± 15.11
	R45	5165.42 ± 1838.66	451.31 ± 148.96	133.56 ± 151.87	24.44 ± 15.03
	R60	5767.58 ± 2088.05	501.72 ± 171.21	121.36 ± 123.14	23.14 ± 14.24
3	Post	4753.97 ± 2412.41	694.83 ± 385.20	193.36 ± 164.26	36.25 ± 15.20
	R15	4189.58 ± 2060.87	459.81 ± 215.83	138.67 ± 115.14	29.78 ± 13.61
	R30	4753.64 ± 2254.38	452.14 ± 200.63	127.50 ± 109.05	26.06 ± 13.77
	R45	5218.06 ± 2431.15	470.56 ± 169.55	114.81 ± 108.62	29.06 ± 14.90
	R60	5780.19 ± 2611.11	502.72 ± 195.92	113.75 ± 109.62	29.58 ± 16.25

Table 14. Multilevel models of endocrine responses and time.

	Cortisol				Epinephrine				Norepinephrine			
	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper
Fixed effect												
Intercept	14.30	2.02	10.34	18.26	70.59	5.20	60.41	80.78	667.39	58.36	553.00	781.78
Baseline	0.30	0.12	0.07	0.53	0.26	0.04	0.18	0.34	0.67	0.09	0.49	0.84
Time	-0.61	0.16	-0.93	-0.30	-36.91	2.76	-42.32	-31.50	-363.05	24.99	-412.02	-314.08
$Time^2$	-0.11	0.03	-0.18	-0.05	5.86	0.61	4.67	7.06	68.57	5.29	58.20	78.93
	Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation	
Random effect												
Visit	12.30	3.51			1357.26	36.84			81637.00	285.72		
Time	0.33	0.57	-0.37		57.64	7.59	-1.00		6359.00	79.74	-1.00	
Subject	6.18	2.49			299.91	17.32			33842.00	183.96		
Time	0.09	0.30	-0.27		21.72	4.66	-0.86		2832.00	53.22	-0.92	
Residual	1.78	1.33			563.32	23.73			42295.00	205.66		

Table 15. Multilevel models of lymphocyte (%) and time.

	CD3				CD4				CD8				CD19				NK Cells			
	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper
Fixed effect																				
Intercept	58.04	2.39	53.36	62.71	30.05	1.86	26.40	33.70	25.32	1.50	22.38	28.27	6.24	0.76	4.75	7.73	20.87	1.29	18.33	23.40
Baseline	0.09	0.03	0.04	0.15	0.10	0.04	0.02	0.17	0.12	0.04	0.04	0.20	0.35	0.04	0.26	0.43	0.11	0.05	0.02	0.21
Time	7.71	0.38	6.95	8.46	8.79	0.36	8.09	9.49	-0.92	0.21	-1.33	-0.50	3.39	0.16	3.08	3.70	-10.93	0.44	-11.79	-10.06
$Time^2$	-1.47	0.08	-1.62	-1.31	-1.56	0.07	-1.70	-1.41	0.08	0.04	0.00	0.15	-0.57	0.03	-0.64	-0.50	2.01	0.09	1.82	2.19
	Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation	
Random effect																				
Visit	10.88	3.30			12.36	3.52			2.39	1.55			2.88	1.70			18.10	4.25		
Time	1.24	1.11	-0.94		1.37	1.17	-0.93		0.20	0.44	-0.53		0.15	0.39	-0.75		1.76	1.33	-0.97	
Subject	49.91	7.06			22.98	4.79			37.56	6.13			2.01	1.42			39.70	6.30		
Time	0.99	0.99	-0.85		0.68	0.82	-0.72		0.63	0.80	-0.76		0.13	0.37	1.00		1.17	1.08	-0.97	
Residual	9.43	3.07			8.28	2.88			2.19	1.48			1.76	1.33			12.87	3.59		

Table 16. Multilevel models of lymphocyte cell counts and time.

	CD3				CD4				CD8				CD19				NK Cells			
	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper
Fixed effect																				
Intercept	1185.65	93.00	1003.38	1367.92	585.28	46.95	493.27	677.30	567.06	42.92	482.94	651.17	189.37	16.99	156.07	222.67	555.37	39.04	478.86	631.88
Baseline	0.28	0.06	0.17	0.39	0.28	0.05	0.18	0.38	0.29	0.05	0.19	0.39	0.29	0.04	0.21	0.38	0.17	0.05	0.06	0.27
Time	-470.56	20.99	-511.69	-429.43	-174.38	8.80	-191.63	-157.14	-286.37	14.01	-313.83	-258.92	-54.77	4.01	-62.63	-46.90	-394.36	17.90	-429.44	-359.29
$Time^2$	81.08	4.43	72.40	89.77	30.29	1.99	26.40	34.19	49.54	2.84	43.98	55.11	9.70	0.84	8.05	11.34	71.58	3.51	64.70	78.46
	Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation	
Random effect																				
Visit	73821.00	271.70			13268.53	115.19			28009.00	167.36			2026.20	45.01			40379.00	200.95		
Time	6139.00	78.35	-0.92		863.00	29.38	-0.79		2494.00	49.94	-0.99		117.90	10.86	-0.70		4022.00	63.42	-1.00	
Subject	44669.00	211.35			6130.37	78.30			24698.00	157.16			2293.10	47.89			30730.00	175.30		
Time	1500.00	38.73	-0.71		23.73	4.87	0.53		1185.00	34.42	-0.93		100.10	10.01	-0.73		2465.00	49.65	-1.00	
Residual	29707.00	172.36			5976.60	77.31			12190.00	110.41			1062.90	32.60			18645.00	136.55		

Table 17. Multilevel models of leukocytes (%) and time.

	Neutrophils				Monocytes				Eosinophils				Basophils			
	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper
Fixed effect																
Intercept	39.86	4.27	9.34	48.22	6.88	0.62	11.18	8.09	0.70	0.21	3.26	1.12	0.37	0.04	9.52	0.44
Baseline	0.34	0.08	4.39	0.49	0.09	0.07	1.26	0.22	0.52	0.03	14.91	0.58	0.18	0.07	2.60	0.32
Time	7.65	0.44	17.26	8.52	-0.67	0.09	-7.38	-0.49	-0.12	0.07	-1.84	0.01	-0.02	0.01	-3.94	-0.01
$Time^2$	-0.97	0.09	-10.29	-0.79	0.10	0.02	4.83	0.14	-0.03	0.01	-2.12	0.00				
	Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation	
Random effect																
Visit	41.01	6.40			1.21	1.10			1.00	1.00			0.01	0.10		
Time	2.69	1.64	-0.39		0.04	0.19	-0.49		0.03	0.18	-0.54		0.00	0.04	-0.59	
Subject	25.38	5.04			2.36	1.54			0.75	0.87			0.01	0.11		
Time	0.58	0.76	-0.05		0.03	0.16	0.11		0.05	0.23	-0.77		0.00	0.01	-0.12	
Residual	13.51	3.68			0.62	0.79			0.23	0.48			0.02	0.15		

Table 18. Multilevel models of leukocyte cell counts and time.

	Neutrophils				Monocytes				Eosinophils				Basophils			
	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper	β	SE	Lower	Upper
Fixed effect																
Intercept	1752.28	364.95	4.80	2467.56	259.05	33.01	7.85	323.76	87.28	15.28	5.71	117.23	25.02	2.54	9.86	29.99
Baseline	0.89	0.10	9.27	1.07	0.73	0.05	13.58	0.83	0.52	0.03	17.73	0.58	0.34	0.07	4.89	0.48
Time	-292.41	82.12	-3.56	-131.45	-161.94	10.51	-15.40	-141.33	-45.53	4.59	-9.91	-36.52	-6.20	1.28	-4.84	-3.69
$Time^2$	160.71	15.99	10.05	192.04	33.80	2.30	14.70	38.31	6.62	0.76	8.67	8.12	1.02	0.30	3.44	1.60
	Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation		Variance	SD	Correlation	
Random effect																
Visit	1205285.00	1097.90			23445.15	153.12			5744.40	75.79			58.50	7.65		
Time	174420.00	417.60	-0.24		1840.30	42.90	-0.86		229.30	15.14	-0.83		7.22	2.69	-0.75	
Subject	359043.00	599.20			3090.29	55.59			4789.00	69.20			41.84	6.47		
Time	24568.00	156.70	0.89		54.12	7.36	-1.00		318.70	17.85	-0.92		1.45	1.21	-0.43	
Residual	386326.00	621.60			7991.19	89.39			880.50	29.67			133.34	11.55		

Table 19. Multilevel models of immunoglobulins-G & -M.

	IgG				IgM			
	β	SE	Lower	Upper	β	SE	Lower	Upper
Fixed effect								
Intercept	80.91	23.65	34.56	127.27	6.87	1.62	3.70	10.05
Baseline	0.98	0.02	0.94	1.02	0.98	0.01	0.95	1.00
Time	-71.97	4.57	-80.92	-63.01	-7.52	0.48	-8.46	-6.58
$Time^2$	13.45	1.05	11.38	15.51	1.44	0.11	1.23	1.65
	Variance	SD	Correlation		Variance	SD	Correlation	
Random effect								
Visit	2579.07	50.79			45.49	6.74		
Time	152.35	12.34	-0.73		2.26	1.50	-0.81	
Subject	46.87	6.85			1.10	1.05		
Time	6.83	2.61	0.91		0.25	0.50	1.00	
Residual	1674.36	40.92			17.47	4.18		

Table 20. Multilevel model of neutrophil function.

	Neutrophil Oxidative Burst			
	β	SE	Lower	Upper
Fixed effect				
Intercept	43.16	5.18	33.01	53.32
Baseline	0.55	0.05	0.44	0.65
Time	0.28	0.13	0.02	0.54
	Variance	SD	Correlation	
Random effect				
Visit	9.22	3.04		
Time	0.24	0.49	-1.00	
Subject	0.26	0.51		
Time	0.00	0.06	-1.00	
Residual	16.35	4.04		

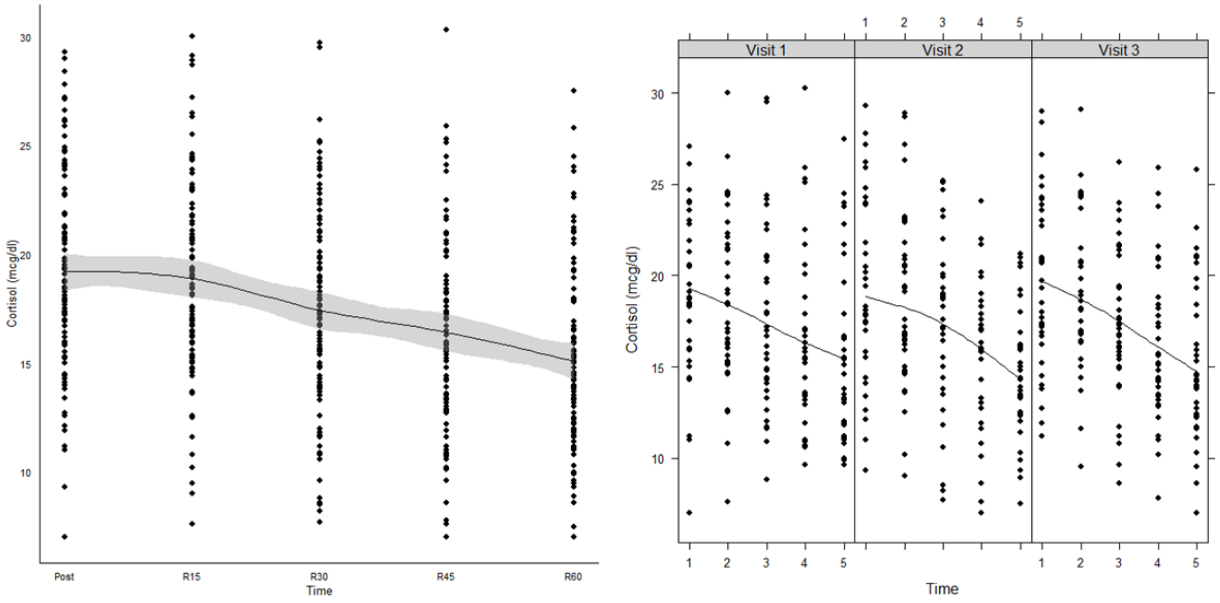

Fig. 1. Summary cortisol responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

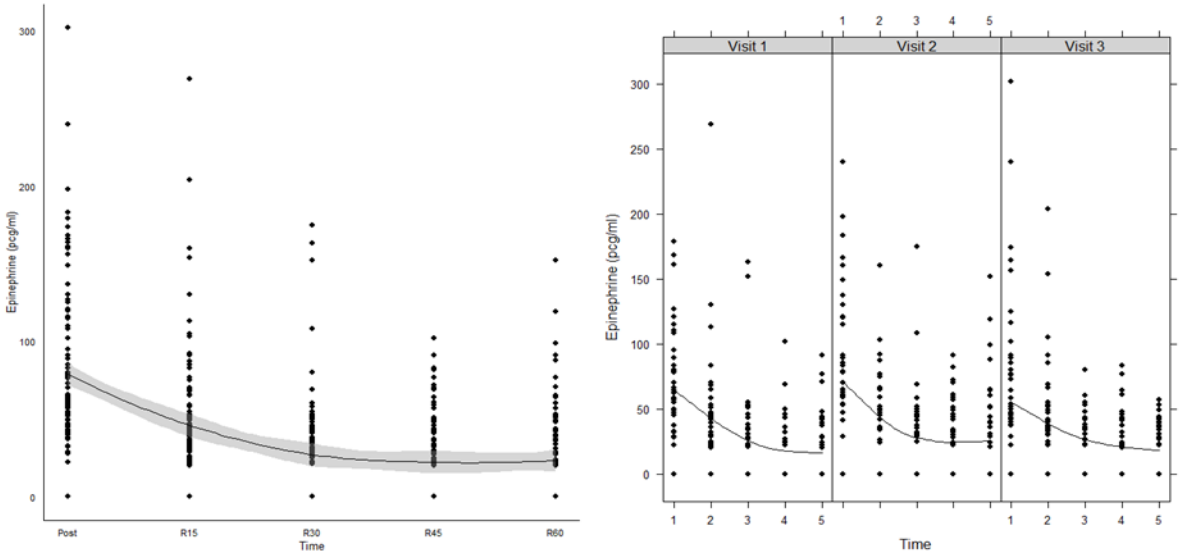

Fig. 2. Summary epinephrine responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

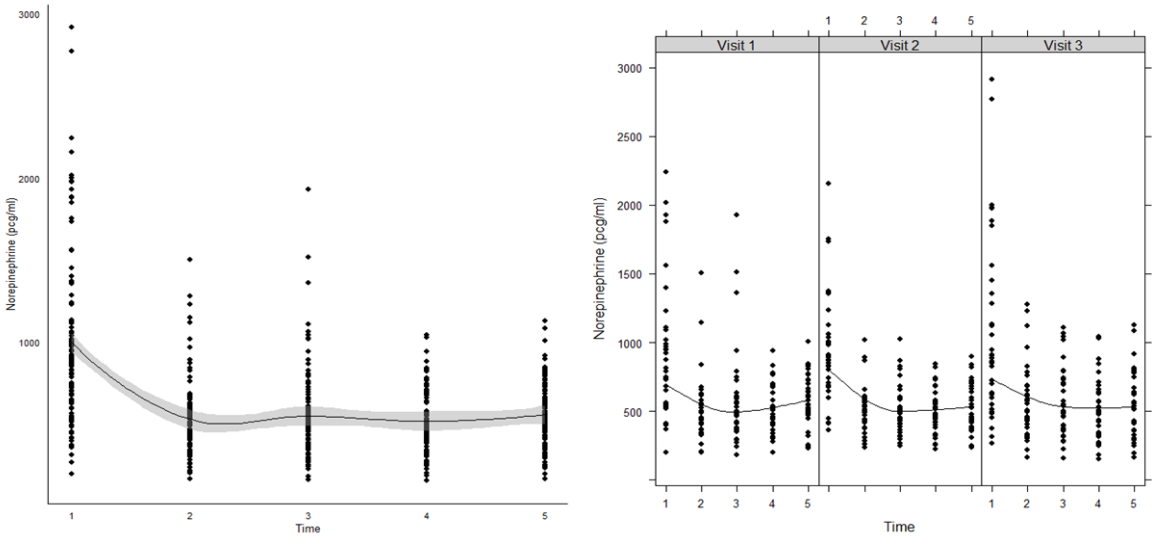

Fig. 3. Summary norepinephrine responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

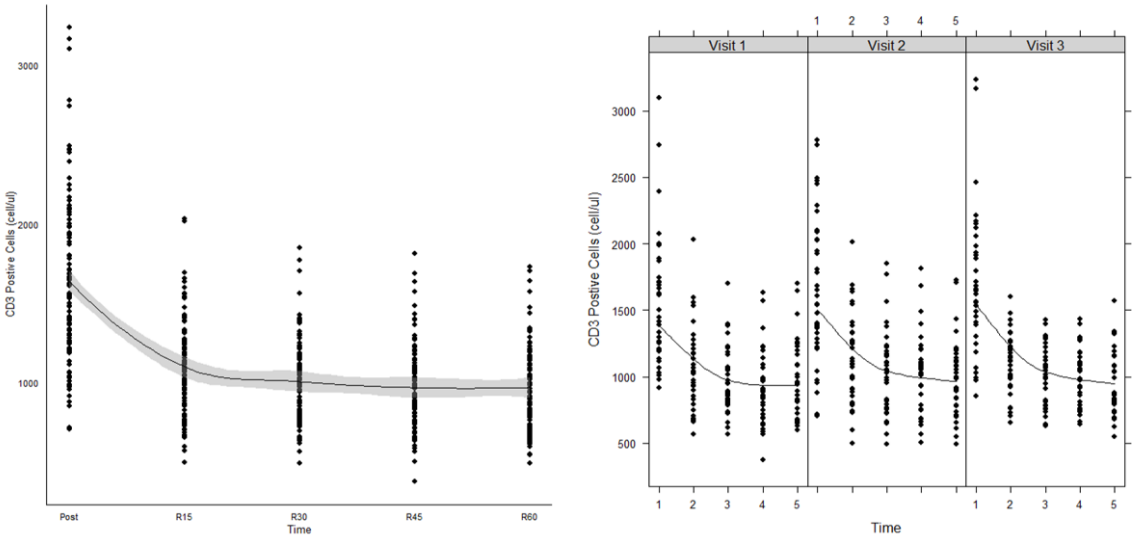

Fig. 4. Summary $CD3^+$ cell responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

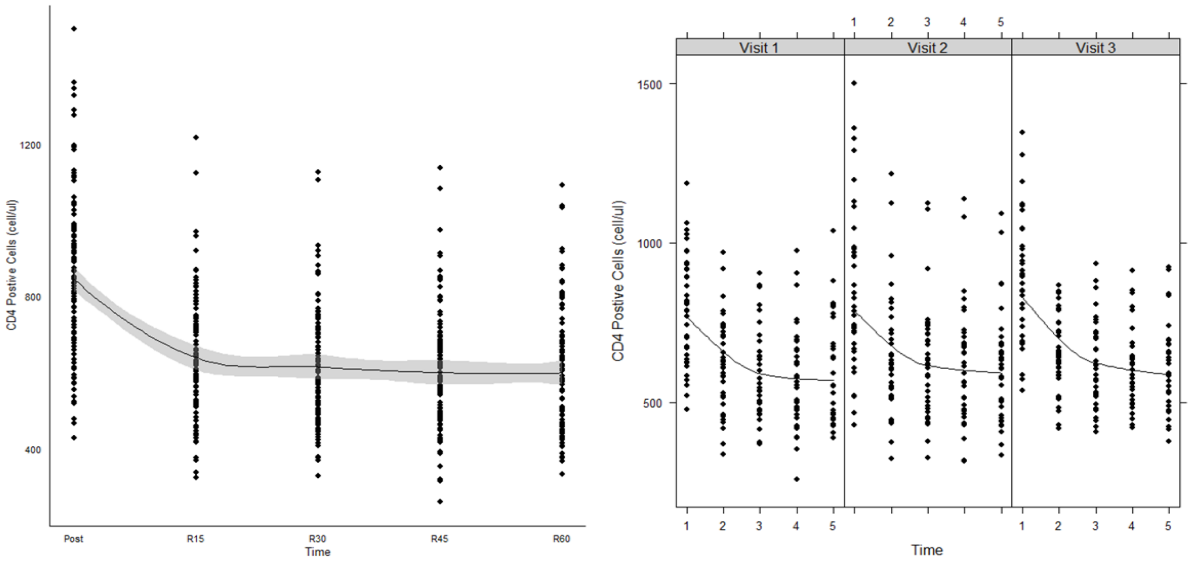

Fig. 5. Summary CD4$^+$ cell responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

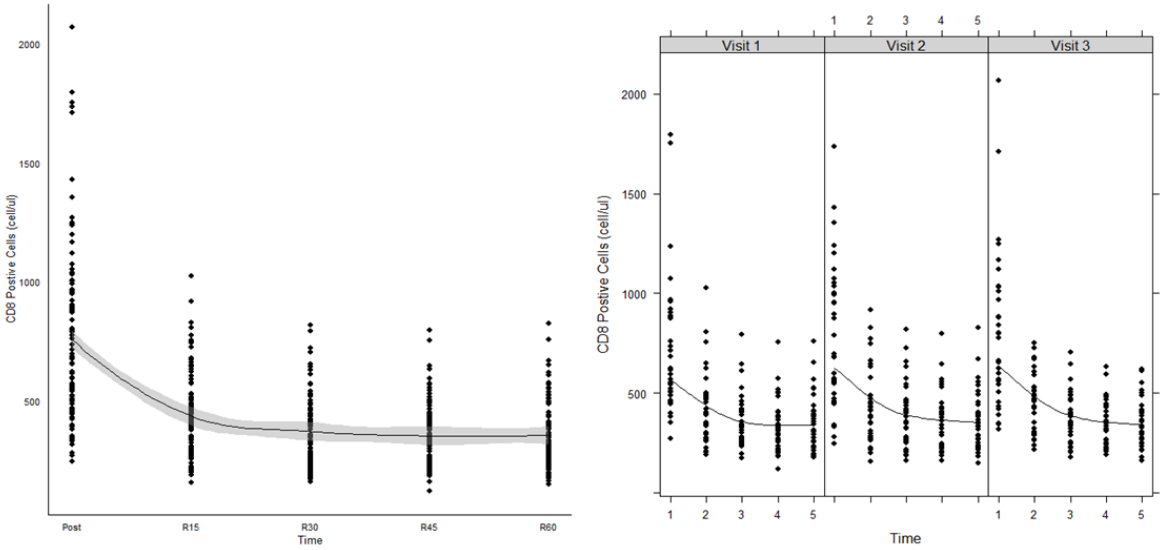

Fig. 6. Summary CD8$^+$ cell responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

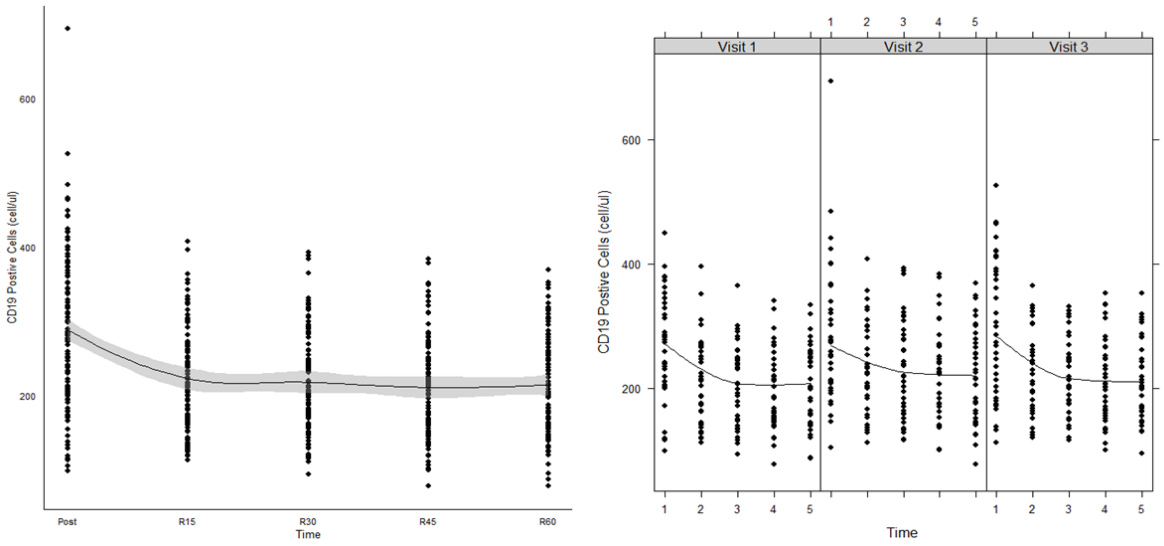

Fig. 7. Summary CD19^{+} cell responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

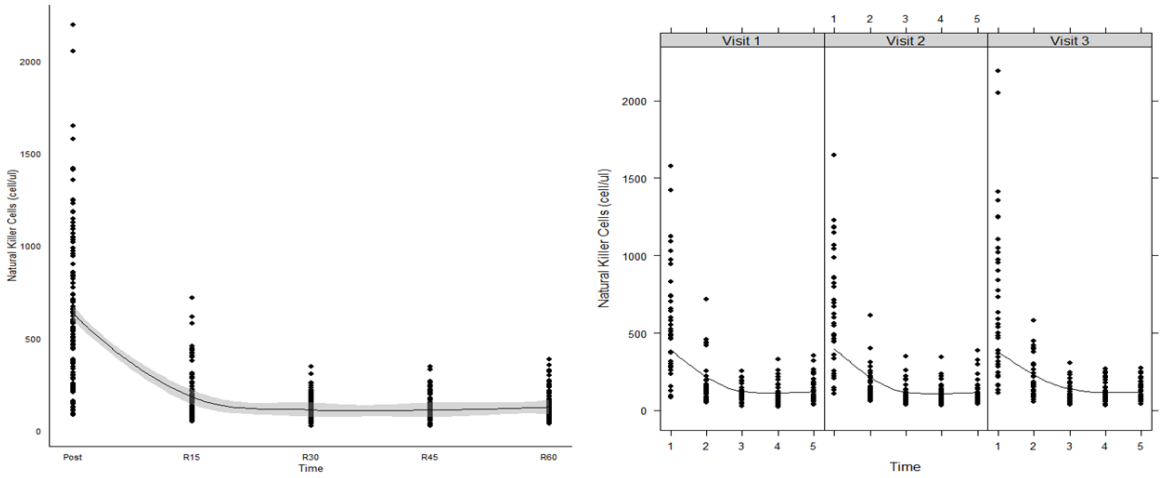

Fig. 8. Summary natural killer cell responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

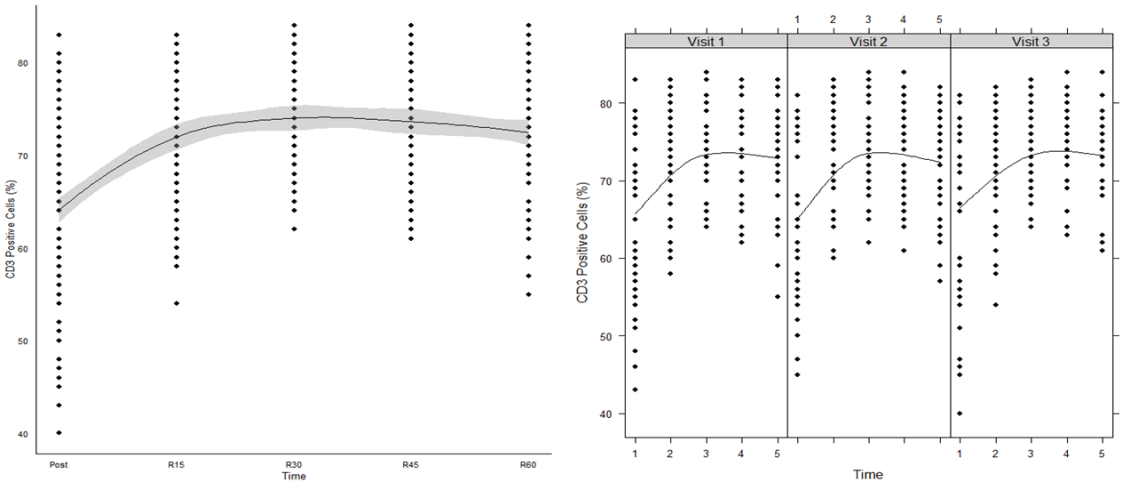

Fig. 9. Summary CD3$^+$ cell responses (%) exhibited a curvilinear increase over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

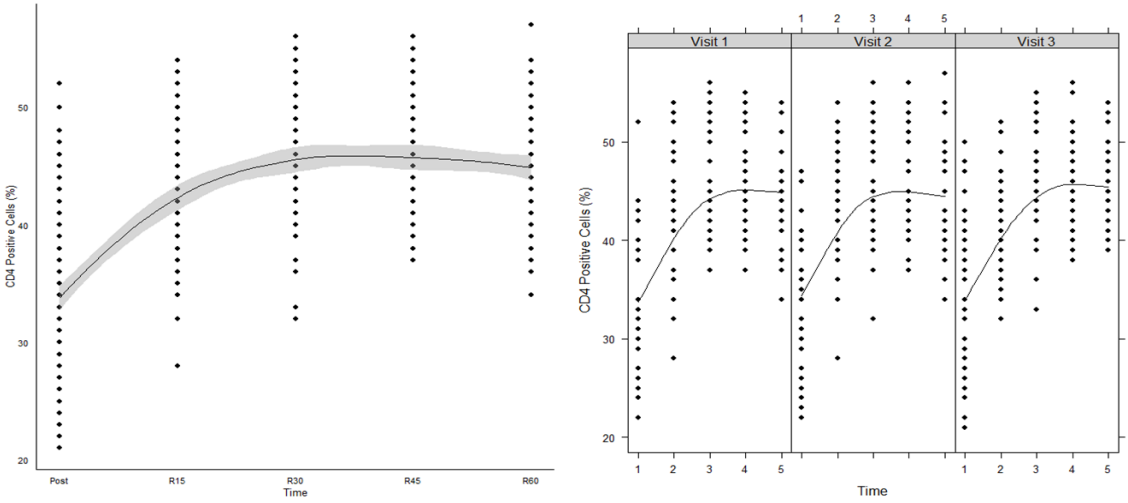

Fig. 10. Summary CD4$^+$ cell responses (%) exhibited a curvilinear increase over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

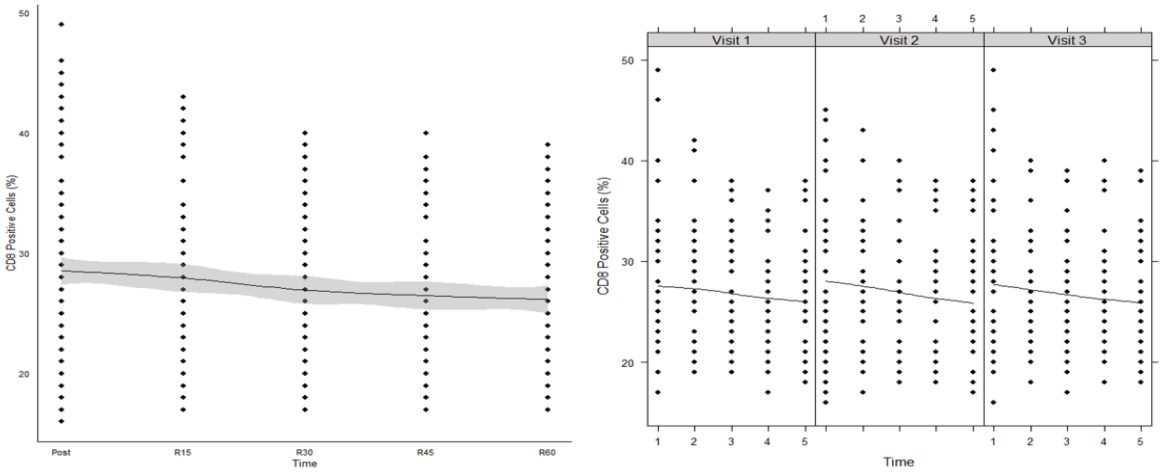

Fig. 11. Summary CD8⁺ cell responses (%) exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

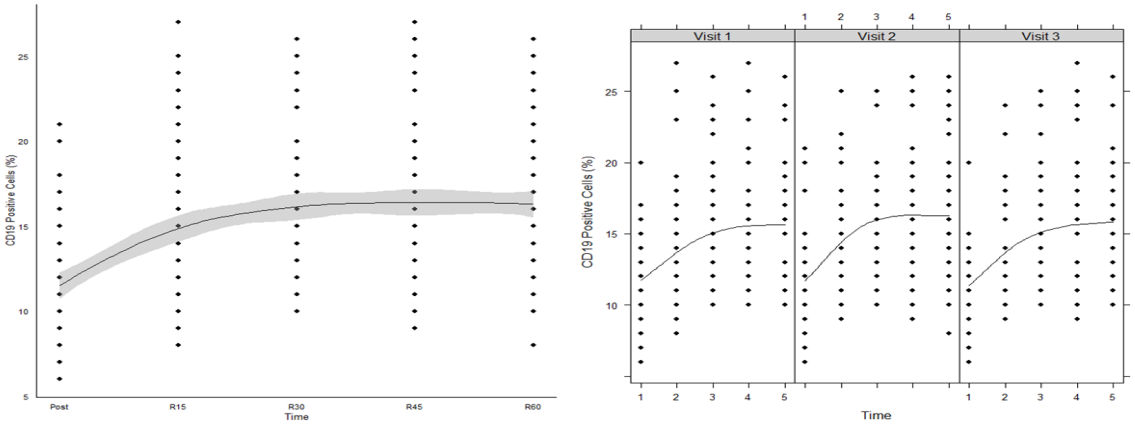

Fig. 12. Summary CD19⁺ cell responses (%) exhibited a curvilinear increase over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

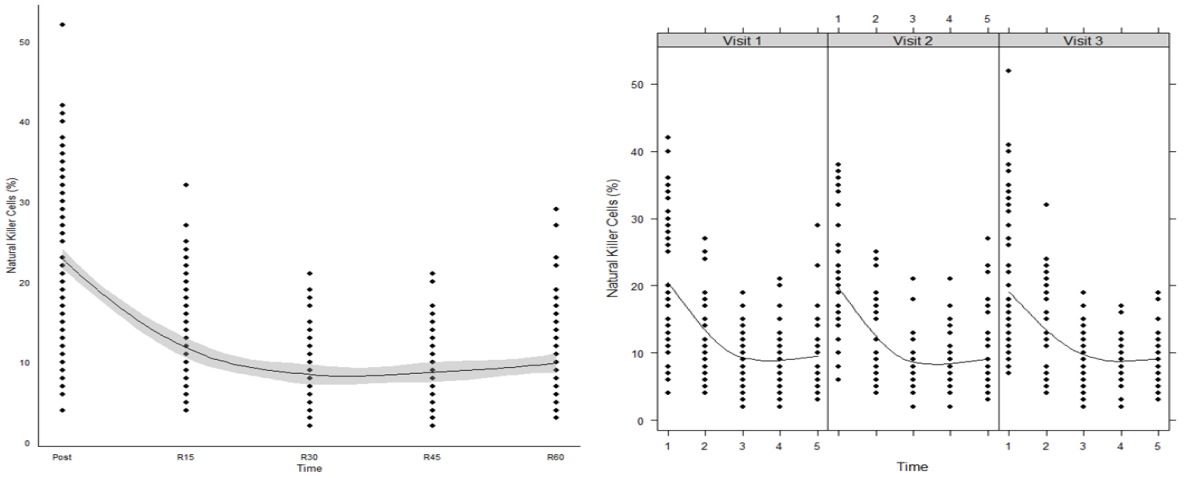

Fig. 13. Summary Natural Killer cell responses (%) exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

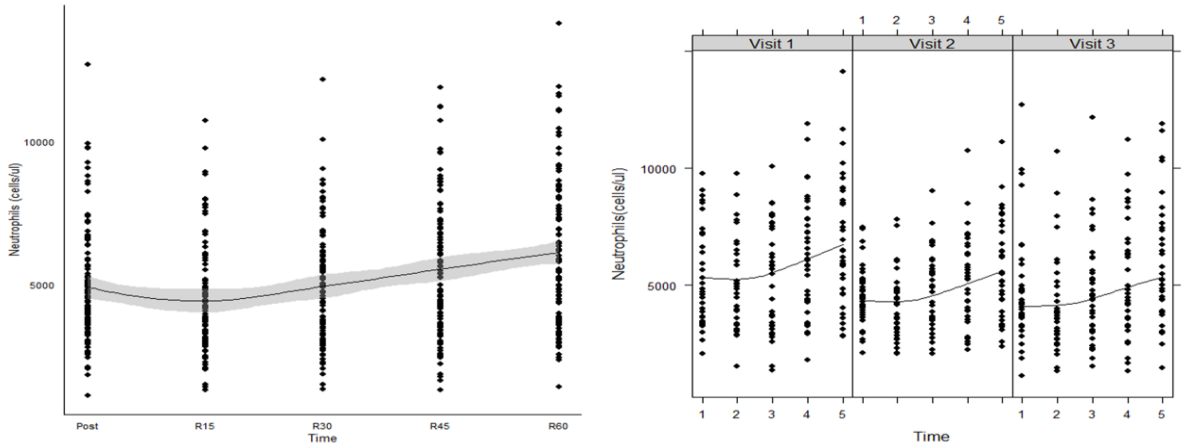

Fig. 14. Summary neutrophil responses exhibited a curvilinear increase over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

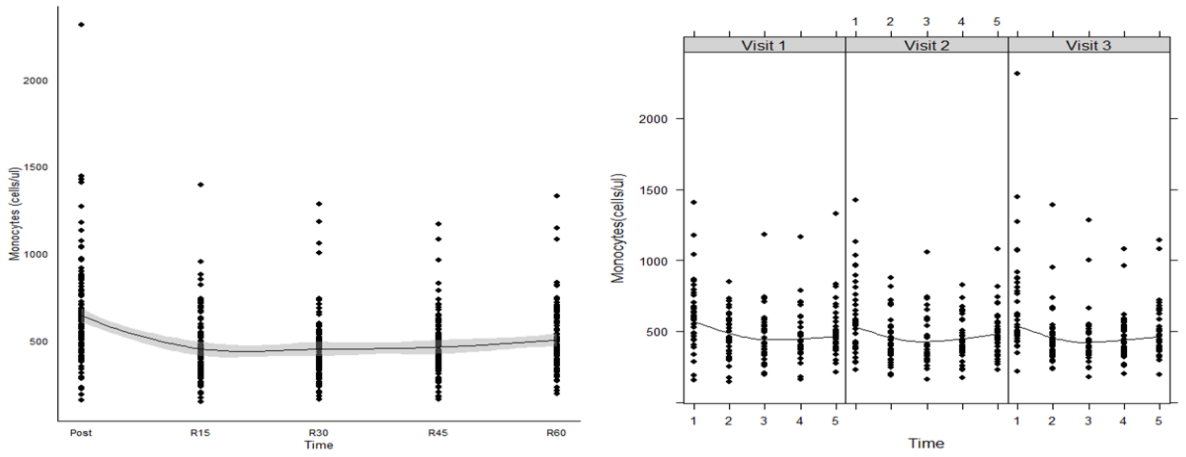

Fig. 15. Summary monocyte responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

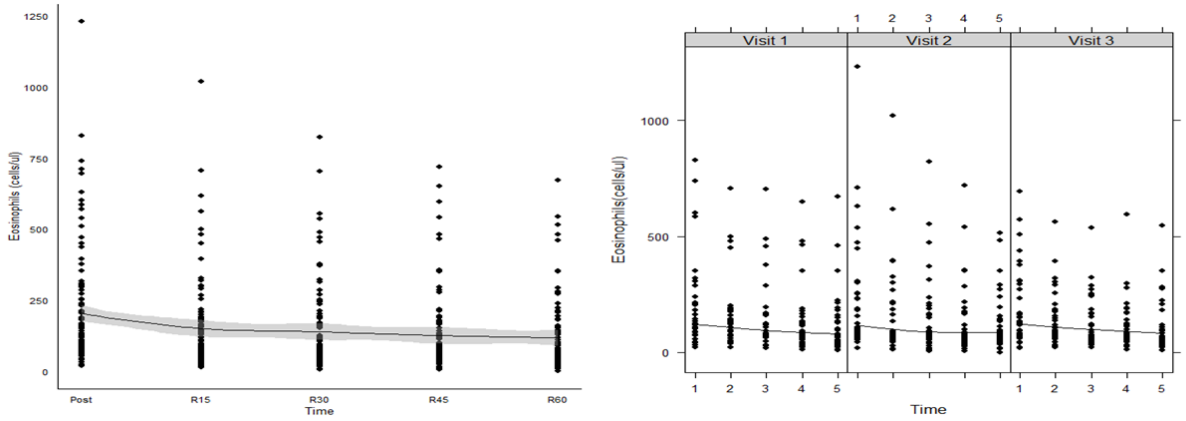

Fig. 16. Summary eosinophil responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

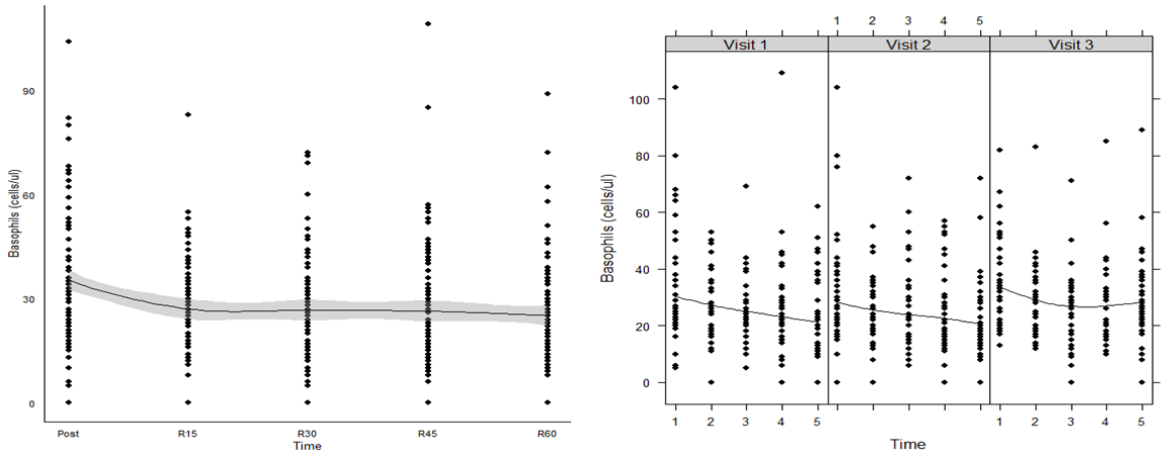

Fig. 17. Summary basophil responses exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

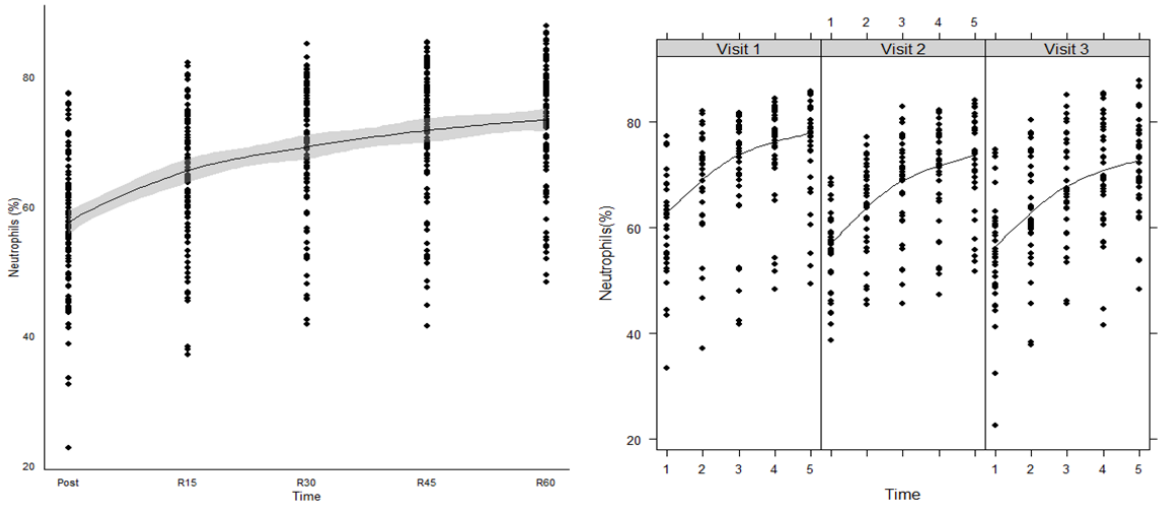

Fig. 17. Summary neutrophil responses (%) exhibited a curvilinear increase over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

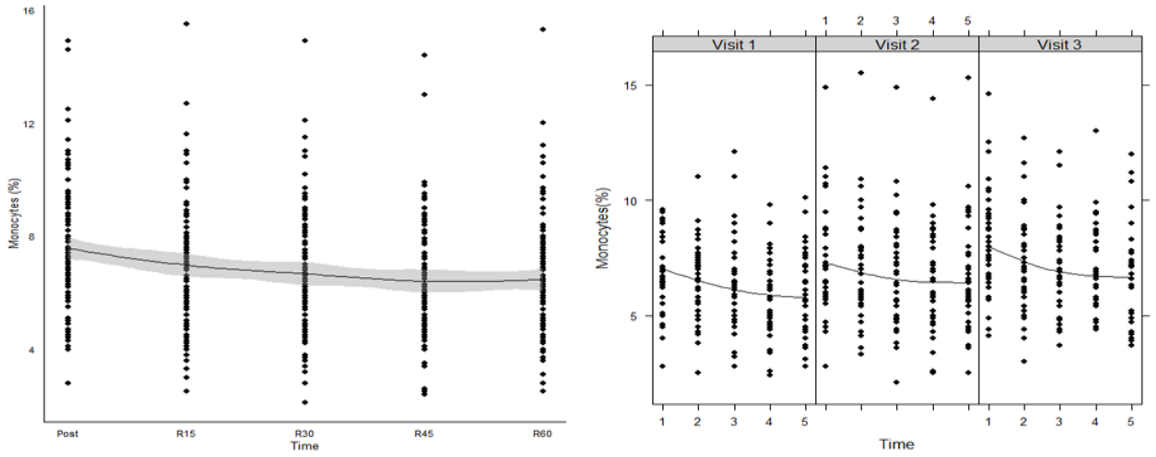

Fig. 18. Summary monocytes responses (%) exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

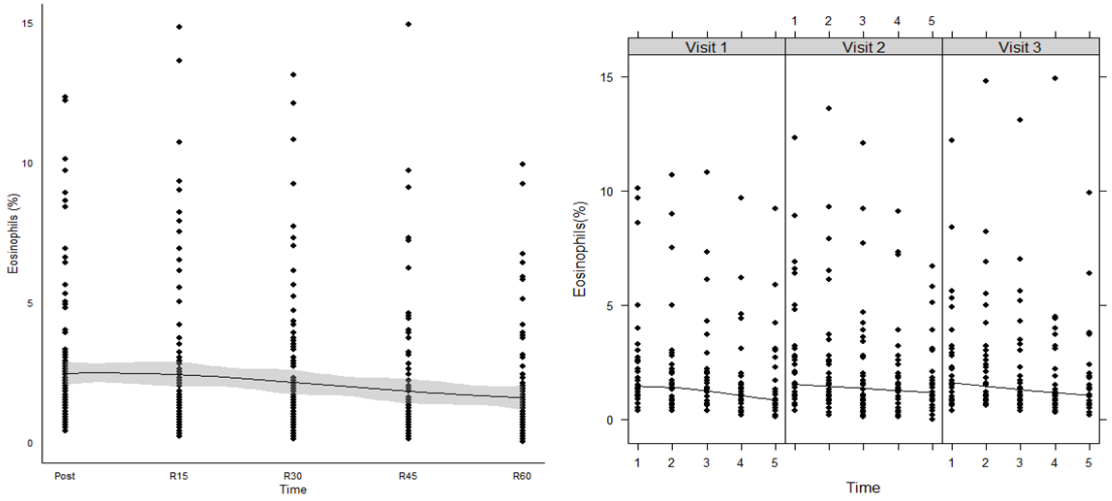

Fig. 19. Summary eosinophil responses (%) exhibited a curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

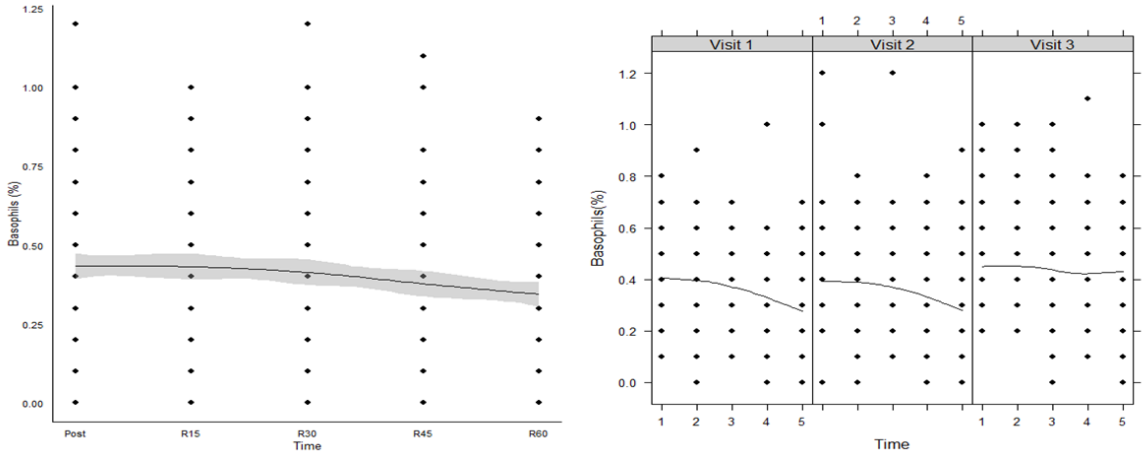

Fig. 20. Summary basophil responses (%) exhibited an approximately linear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

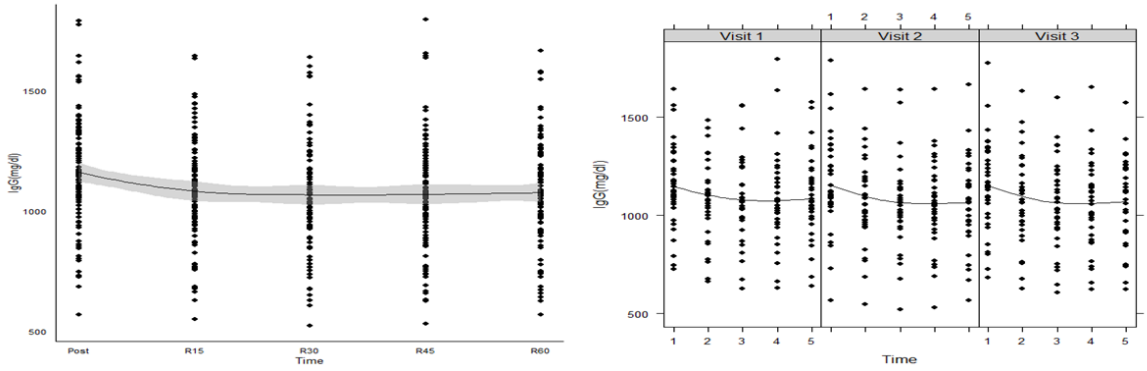

Fig. 21. Summary IgG responses exhibited curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

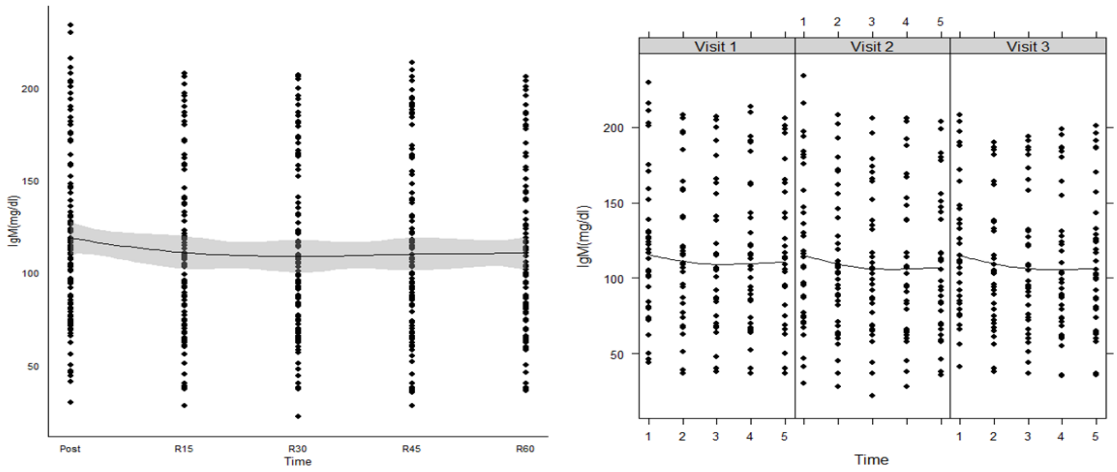

Fig. 22. Summary IgM responses exhibited curvilinear decrease over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

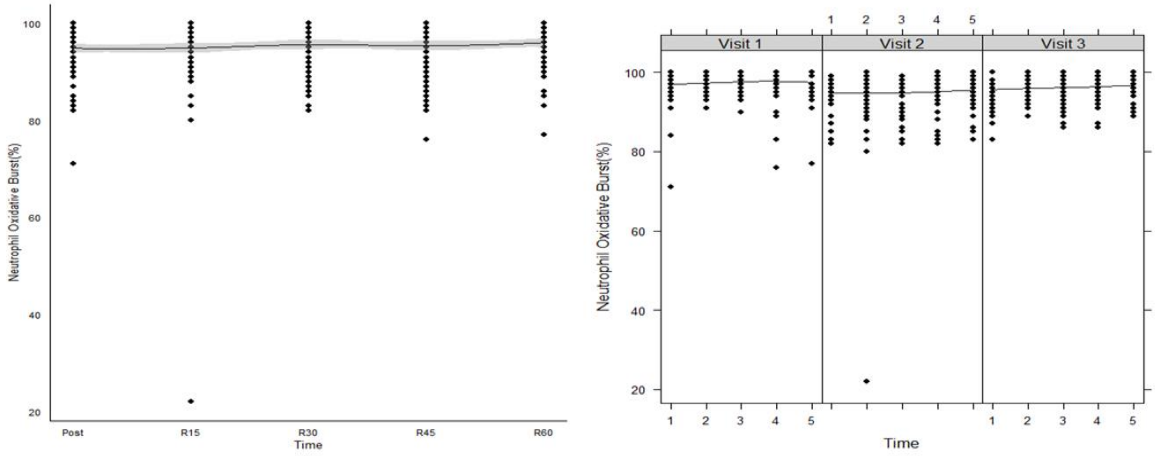

Fig. 23. Summary neutrophil oxidative burst responses (%) exhibited an approximately linear increase over time. (*l.*) Locally weighted regression line using all data points in the analysis. Shaded area indicates 95% confidence interval. (*r.*) Locally weighted regression lines presented for each visit.

Cortisol (mcg/dl)	Baseline	IP	R15	R30	R45	R60
B01-1.1	20.6	19.5	22.3	18	17	15.5
B01-1.2	9.9	27.2	26.3	24.7	19.9	18
B01-1.3	13.3	14	16.9	14	12.2	9.5
E02-1.1	22.6	26.1	24.6	20.8	18.8	19.6
E02-1.2	16.6	18.1	20.5	19.3	17.9	15.9
E02-1.3	16.3	17.2	18.9	17.3	15.7	14
Z03-1.1	22.7	24.7	30	29.5	30.3	24.5
Z03-1.2	19.6	21.2	20.9	18.8	17	16
Z03-1.3	22.4	22.7	20.7	17.4	18.4	15.3
G04-1.1	10.9	21.9	24.5	24.4	22.5	19.6
G04-1.2	14	20.5	19.4	17.2	15.8	13.7
G04-1.3	16.7	23	20.8	19.4	17.4	15.9
P05-1.1	15.7	23.6	21.5	19.6	17.9	15.1
P05-1.2	14.4	26.2	28.7	25.2	21.7	20.5
P05-1.3	13	20.8	16.8	17.1	12.9	12.2
P06-1.1	15.7	11.2	10.8	8.8	9.6	9.9
P06-1.2	18.1	14.1	12.5	10.6	8.6	7.5
P06-1.3	12.3	17.7	19.8	15.6	14.3	14.2
G07-1.1	11.6	7	7.6	10.9	11	10.8
G07-1.2	12.1	12.1	10.2	8.2	7	7.5
G07-1.3	13.4	11.2	9.5	8.6	7.8	7
R08-2.1	11.2	24	26.5	29.7	25.3	23.8
R08-2.2	16.5	27.8	28.9	25.1	24.1	20.7
R08-2.3	17.2	16.2	20.5	21.6	18.2	17.8
R09-2.1	18.5	23	22.1	21	17.1	16.7
R09-2.2	16.3	15.8	14.6	12.6	11.6	11.4
R09-2.3	21.1	23.6	24.4	23.6	21.6	21.1
W10-2.1	15.4	17.5	14.6	18.5	15.4	13.8
W10-2.2	19.4	12.6	17.6	20.1	17.9	15.2
W10-2.3	12.9	17.3	17	15.4	13.2	10.3
S11-3.1	22.4	15.3	15.1	13.3	13.6	11.9
S11-3.2	18.6	19.4	15.9	13.5	11.9	
S11-3.3	16.5	16.7	16.8	15	14.8	14.6
T12-3.1	19.9	15	16.9	14.8	13.5	11.8
T12-3.2	19.7	18.1	20.6	18.7	18.3	14.8
T12-3.3	18.4	24.2	24.3	23	20.9	21
C13-3.1	14.8	11	12.5	12	10.7	10
C13-3.2	21	14.4	14.7	8.5	10.1	8.9
C13-3.3	20.3	20.9	18.9	18.7	18.8	15.6
W14-3.1	19	18.3	21.4	24.2	25.1	24
W14-3.2	15	19.4	21.8	19	17.6	15
W14-3.3	12.3	19.7	21.5	19.3	17.8	16.2
X15-3.1	18.4	20.6	19.2	17.9	16.7	15.9
X15-3.2	20.3	21.8	21.1	19.9	17.9	16.1
X15-3.3	16.8	20.7	17.5	16.8	15.1	13.8
Y16-3.1	14	18.5	18.5	15.7	15.2	13.2
Y16-3.2	11.7	18.1	16.5	16.8	15.9	13.3
Y16-3.3	14.3	16.9	16.4	17.6	13.9	14.2
Z17-3.1	16	16	16.5	14.3	13.2	11.2

Cortisol (mcg/dl)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	21.3	19.8	20.2	16.4	15.4	13.5
Z17-3.3	18.2	18	15	16.1	15.2	14.3
A18.01	16.8	18.8	20.7	19.8	16.7	15.4
A18.02	14.8	14.4	13.6	13.8	13	9.9
A18.03	24.7	25.4	23.7	21.7	20.5	19.8
B19.01	17.9	18.8	19.9	22.5	25.3	22.8
B19.02	19	17.8	16.7	17.6	16	14.3
B19.03	17.4	23.9	24.6	22.3	21	20.7
D21.01	16.8	18.5	19	17	15.8	15.1
D21.02	18.4	20.2	19.3	19	17.1	14.4
D21.03	20.1	29	29.1	26.2	25.9	25.8
E22.01	17.3	14.4	16.2	14.4	12.9	11.1
E22.02	20.5	11	17.2	17.1	16.3	14.3
E22.03	17.9	24.3	24.6	21.4	20.9	19.3
J24.01	20.8	19.1	17.1	17	15.5	16.5
J24.02	22.3	25.9	23	20.6	22	21.2
J24.03	13.4	26.6	24.5	17.7	21	18.4
K25.01	23.6	22.8	21.7	21	20.6	19.6
K25.02	18.5	24.8	20.9	18.9	17.3	16.2
K25.03	20.9	28.4	24.3	21.1	23.8	21.5
M26.01	18.3	24.1	22.9	21.1	20.1	17.9
M26.02	20.3	29.3	27.2	23.2	24.1	19.2
M26.03	22.2	14.5	15.4	10.8	12.8	11.7
P27.01	15.8	15.9	15.2	14.1	13.4	13
P27.02	16.6	17.5	16.2	15	13.3	12.4
P27.03	15	13.8	11.6	9.6	11.2	10.3
R28.01	13.5	18.4	16.3	13.7	13.6	13.5
R28.02	15.9	23.9	23.1	22	20.2	18.9
R28.03	11.1	15.2	16.3	11.7	14.4	11.6
Z29.01	19.7	24	24.4	23.9	21.7	21.2
Z29.02	13.9	24.3	22.9	23.6		21
Z29.03	20.7	24.9	25.5	24	24.5	22.6
A30.01	17.4	18.7	14.7	11.6	10.9	13.3
A30.02	17.7	18.3	15	14.4	12.7	12.3
A30.03	13.9	21	18.1	15.8	13.4	13
B31.01	13.1	20.6	20.7	16.7	16.7	14.6
B31.02	10.5	24	23.2	20.6	18.6	16.9
B31.03	13.3	19.3	19.8	18.1	17.2	14.6
C32.01	13.1	20.5	16	15.4	13.4	12
C32.02	14	17.4	14.8	13.5	12.7	12
C32.03	18.2	20.9	19.1	16.7	15.1	12.3
D33.01	20.1	16.4	18.4	17.2	16	21.7
D33.02	13.7	14.4	16.8	18.3	19	16.2
D33.03	14.1	11.9	14.4	14.9	13.5	12.4
H34.01	15.7	21.3	17.4	16.1	14.4	13.8
H34.02	13.2	15.5	13.7	11.8	10.8	10.3
H34.03	10.9	18.5	16.3	13.9	11	11.1
J35.01	12.7	14.3	12.6	11.7	10.6	9.6
J35.02	13.6	13.4	19.1	18.7	16.3	13.4

Cortisol (mcg/dl)	Baseline	IP	R15	R30	R45	R60
J35.03	18.2	16.7	18.2	17.6	15.6	13.9
K36.01	13.8	18.7	15.6	14.9	11.9	11
K36.02	15.4	9.3	9	7.7	7.6	7.5
K36.03	10.9	12.7	13.7	11.2	10.2	8.6
M37.01	16	18.3	15.3		16.3	16.6
M37.02	17.7	17	16.9	15.5	13	12.5
M37.03	16.1		18.6	16	14.2	12.7
O38.01	17.2	27.1	23.9	22.8	25.9	27.5
O38.02	20.6	17.9	16.4	16.8	14.3	13.9
O38.03	18.8	21	17.5	16.3	16.5	14.5

Epinephrine (pcg/ml)	Baseline	IP	R15	R30	R45	R60
B01-1.1	53	70	29	0	0	28
B01-1.2	56	78	49	30	42	39
B01-1.3	0	37	23	0	21	0
E02-1.1	52	121	83	55	27	42
E02-1.2	39	70	42	48	46	39
E02-1.3	28	42	37	31	29	22
Z03-1.1	25	95	83	46	50	0
Z03-1.2	37	47	34	25	24	24
Z03-1.3	29	40	30	27	24	0
G04-1.1	0	29	25	21	0	0
G04-1.2	0	54	24	0	22	21
G04-1.3	0	54	37	34	0	0
P05-1.1	0	33	23	27	0	0
P05-1.2	28	83	47	69	49	36
P05-1.3	25	43	36	26	24	0
P06-1.1	25	28	43	28	22	0
P06-1.2	0	29	35	0	0	0
P06-1.3	38	164	69	55	46	57
G07-1.1	0	37	47	21	36	28
G07-1.2	27	53	45	32	28	0
G07-1.3	27	22	42	23	0	0
R08-2.1	30	168	113	51	50	44
R08-2.2	0	166	103	44	44	64
R08-2.3	30	102	53	42	32	28
R09-2.1	0	22	21	0	0	0
R09-2.2	0	0	0	0	0	0
R09-2.3	0	0	23	0	0	0
W10-2.1	60	62	46	31	22	0
W10-2.2	42	120	77	41	23	31
W10-2.3	49	38	0	0	0	0
S11-3.1	0	45	32	0	24	0
S11-3.2	37	85	65	35	0	
S11-3.3	0	0	0	0	0	0
T12-3.1	53	110	47	43	32	24

Epinephrine (pcg/ml)	Baseline	IP	R15	R30	R45	R60
T12-3.2	91	89	75	46	82	88
T12-3.3	36	47	0	0	0	
C13-3.1	53	49	39	31	36	0
C13-3.2	66	160	52	0	34	99
C13-3.3	33	40		0	0	0
W14-3.1	0	179	58	35	69	48
W14-3.2	27	85	59	37	57	29
W14-3.3	0	29	31	0	0	0
X15-3.1	48	108	47		43	39
X15-3.2	77	115	103	50	70	60
X15-3.3	0	64	41	38	23	31
Y16-3.1	0	50	22	27	0	28
Y16-3.2	47	85	0	52	61	51
Y16-3.3	0	0	0	0	0	0
Z17-3.1	29	79	68	52	46	43
Z17-3.2	77	121		108	91	65
Z17-3.3	80	76	0	26	77	36
A18.01	0	66	0	0	0	0
A18.02	0	0	0	0	0	0
A18.03	24	85	49	36	0	0
B19.01	30	115	269	38		0
B19.02	0	65	36	0	0	0
B19.03	39	240	91	53	48	44
D21.01	0	57	0	0	0	0
D21.02	47	53	0	0	33	0
D21.03	0	302	204	48	41	53
E22.01	0	32	22	0	0	0
E22.02	0	29	0	0	0	44
E22.03	0	89	52	26	37	0
J24.01	0	78	65	23	25	37
J24.02	423	183	160	175	59	152
J24.03	53	116	85	80	83	39
K25.01	0	80	46	0	0	0
K25.02	0	63	26	0	0	0
K25.03	0	45	55	35	0	0
M26.01	122	127	30	38	22	
M26.02	103	137	66	31	0	119
M26.03	32	46	41	0	29	37
P27.01	68	64	45	0	0	22
P27.02	49	79	42	0	0	40
P27.03	0	52	40	22	42	43
R28.01	0	161	130	163	102	77
R28.02	0	240	87	58	72	36
R28.03	27	50	33	35	0	34
Z29.01	42	70	44	0	0	48
Z29.02	43	198	26	45		0
Z29.03	38	156	66	0	43	27
A30.01	69	0	51	34	0	29
A30.02	27	91	0	0	0	0

Epinephrine (pcg/ml)	Baseline	IP	R15	R30	R45	R60
A30.03	39	80	31	22	20	23
B31.01	36	108	53	35	0	28
B31.02	29	130	92	0	30	0
B31.03	32	77	41	0	0	0
C32.01	37	58	70	22	0	0
C32.02	0	149	50	0	51	29
C32.03	0	85	34	0	22	40
D33.01	53	83	58	22	22	0
D33.02	0	59	36	0	0	0
D33.03	37	174	105	60	61	42
H34.01	41	47		0	0	0
H34.02	0	61	47	29	0	0
H34.03	0	125	35	43	0	0
J35.01	25	83	20	28	0	20
J35.02	0	0	0	0	0	0
J35.03	0	73	47	43	61	49
K36.01	29	55	0	0	0	0
K36.02	0	60	0	48	0	0
K36.03	0	43	25	0	0	0
M37.01	0	89	42		0	71
M37.02	0	41	0	0	0	52
M37.03	30		154	53	64	34
O38.01	0	0	24		0	0
O38.02	0	0	0	0	0	0
O38.03	51	58	23	0	0	0

Norepinephrine (pg/ml)	Baseline	IP	R15	R30	R45	R60
B01-1.1	544	411	331	382	533	523
B01-1.2	416	824	419	410	424	414
B01-1.3	391	598	302	313	324	325
E02-1.1	419	922	549	789	778	1009
E02-1.2	324	1058	500	322	331	414
E02-1.3	364	623	427	389	326	353
Z03-1.1	267	748	499	370	399	448
Z03-1.2	288	1062	427	430	381	355
Z03-1.3	281	824	442	358	272	267
G04-1.1	255	538	434	589	682	647
G04-1.2	270	444	419	494	566	683
G04-1.3	358	850	507	321	421	519
P05-1.1	208	368	336	296	276	252
P05-1.2	348	874	431	363	300	309
P05-1.3	255	313	283	279	245	250
P06-1.1	149	549	366	291	399	321
P06-1.2	256	705	542	411	414	452
P06-1.3	347	1354	492	400	339	364
G07-1.1	158	197	202	241	336	344
G07-1.2	258	413	381	383	465	383

Norepinephrine (pg/ml)	Baseline	IP	R15	R30	R45	R60
G07-1.3	217	373	215	225	183	196
R08-2.1	739	2243	1504	940	765	834
R08-2.2	505	1732	1018	825	689	712
R08-2.3	315	1561	651	503	391	567
R09-2.1	772	1928	1147	725	687	641
R09-2.2	323	866	371	385	472	451
R09-2.3	387	1981	1279	795	657	555
W10-2.1	137	399	205	182	201	241
W10-2.2	302	595	237	249	253	250
W10-2.3	180	264	165	159	153	166
S11-3.1	616	1088	555	750	694	773
S11-3.2	628	893	514	520	737	
S11-3.3	398	515	434	647	479	636
T12-3.1	299	2018	655	475	534	541
T12-3.2	832	1369	870	1024	821	578
T12-3.3	450	547	784	1064	1028	
C13-3.1	267	871	445	466	444	730
C13-3.2	217	416	281	295	478	522
C13-3.3	463	721		466	573	1083
W14-3.1	347	748	628	552	529	547
W14-3.2	328	1371	545	504	744	461
W14-3.3	303	453	332	483	477	538
X15-3.1	494	1111	555		633	700
X15-3.2	730	1360	892	805	843	739
X15-3.3	664	634	553	790	690	748
Y16-3.1	201	648	433	501	479	600
Y16-3.2	335	897	505	515	553	660
Y16-3.3	517	460	483	744	712	790
Z17-3.1	555	991	547	490	399	640
Z17-3.2	567	1125		760	687	638
Z17-3.3	677	944	761	1109	843	1129
A18.01	535	1399	675	568	534	577
A18.02	844	891	657	678	573	594
A18.03	744	910	680	696	640	667
B19.01	426	1880	527	609		614
B19.02	653	1238	583	583	630	594
B19.03	374	2771	826	574	782	812
D21.01	231	972	401	349	311	520
D21.02	574	644	417	409	528	546
D21.03	301	1886	653	539	486	638
E22.01	573	1228	489	565	771	827
E22.02	781	677	528	868	580	840
E22.03	440	1452	687	708	627	794
J24.01	408	680	417	425	415	810
J24.02	475	801	598	495	521	895
J24.03	321	1134	586	549	435	425
K25.01	446	944	409	476	515	725
K25.02	361	982	443	454	513	723
K25.03	353	550	427	457	509	618

Norepinephrine (pg/ml)	Baseline	IP	R15	R30	R45	R60
M26.01	413	952	672	635	474	
M26.02	298	874	490	657	731	475
M26.03	235	702	323	281	262	291
P27.01	547	1016	613	595	699	662
P27.02	362	832	566	528	550	578
P27.03	384	883	444	456	423	558
R28.01	467	1558	487	476	459	501
R28.02	400	685	506	439	563	478
R28.03	300	905	382	354	313	409
Z29.01	460	534	450	475	578	765
Z29.02	439	359	257	401		434
Z29.03	421	1851	587	373	323	414
A30.01	473	811	839	1515	942	471
A30.02	505	1752	607	595	689	819
A30.03	712	2000	1118	1016	1044	775
B31.01	288	530	364	409	403	487
B31.02	329	1357	469	483	439	529
B31.03	441	859	557	490	529	517
C32.01	360	731	262	353	449	500
C32.02	379	2158	573	600	480	420
C32.03	377	1977	571	727	569	624
D33.01	641	788	406	603	676	660
D33.02	474	910	377	343	334	378
D33.03	365	1054	401	483	477	512
H34.01	150	517		270	201	230
H34.02	220	849	379	268	226	238
H34.03	220	2918	619	543	341	301
J35.01	351	734	577	467	439	604
J35.02	346	997	499	401	451	446
J35.03	322	1286	965	1042	879	916
K36.01	638	876	341	369	304	484
K36.02	309	1039	375	407	322	370
K36.03	488	1123	607	465	496	555
M37.01	587	539	540		833	844
M37.02	603	1005	560	593	684	724
M37.03	612		1229	889	1043	804
O38.01	444	563	323		364	505
O38.02	300	739	340	315	257	433
O38.03	303	495	316	363	318	428

$CD3^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	1457	1116	971	956	862	939
B01-1.2	1326	2492	1257	1086	1057	987
B01-1.3	1422	1487	1083	1076	1055	1151
E02-1.1	1393	1207	899	787	693	647
E02-1.2	1419	2288	1246	1161	1298	1204
E02-1.3	1530	1302	1260	1252	1148	1080
Z03-1.1	1437	1869	1277	819	854	810
Z03-1.2	1138	1610	883	829	634	736
Z03-1.3		1915	1139	911	860	800
G04-1.1	1400	1418	1179	957	888	831
G04-1.2	978	1256	1072	991	1010	995
G04-1.3	1357	2118	1214	985	985	813
P05-1.1	1226	1011	1041	880	835	816
P05-1.2	1530	2744	1637	1376	1103	1174
P05-1.3	1497	1559	1427	1304	1270	1194
P06-1.1	2139	1886	1598	1218	1572	1704
P06-1.2	2121	2780	2016	1852	1812	1728
P06-1.3	1651	2464	1326	1146	1150	1152
G07-1.1	1507	1716	1415	1399	1367	1473
G07-1.2	1456	1945	1544	1406	1396	1436
G07-1.3	1799	1933	1477	1283	1432	1572
R08-2.1	1096	1710	1089	856	746	673
R08-2.2	1171	1549	983	729	681	614
R08-2.3	1070	1683	1141	945	919	872
R09-2.1	1126	1710	1028	831	789	722
R09-2.2	1378	1541	1136	1160	1022	1110
R09-2.3	1524	1981	1600	1182	1100	1043
W10-2.1	686	916	570	568	565	599
W10-2.2	700	706	501	495	507	496
W10-2.3	846	976	655	633	642	622
S11-3.1	1405	1612	928	1045	1092	1195
S11-3.2	1618	1220	1094	1190	1062	
S11-3.3	1160	1064	1003	1075	1061	1077
T12-3.1	1158	1500	957	867	842	763
T12-3.2	1156	957	1006	976	928	895
T12-3.3	1507	1029	1006	1001	970	876
C13-3.1	1405	1746	1068	976	1199	
C13-3.2	1505	1208	999	1031		714
C13-3.3	1777	1306	987	996	973	1044
W14-3.1	1290	1337	1209	835	604	
W14-3.2	1358	2472	1386	1153	1086	1031
W14-3.3	1390	1450	1117	984	882	838
X15-3.1	1179	1193	687	619	377	653
X15-3.2	1375	1327	741	662	663	655
X15-3.3	1078	856	729	700	742	791
Y16-3.1	1558	1988	1314	1228	807	1229
Y16-3.2	1744	2100	1219	1108	1097	1121
Y16-3.3	2035	1646	1393	1398	1399	1331
Z17-3.1	1735	2393	673	1385	1226	1248

$CD3^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	1929	2028		1236	1127	1085
Z17-3.3	1622	1392	1257	1309	1176	1230
A18.01	2562	3100	2033	1704	1634	1643
A18.02	2618	2090	1692	1772	1686	1706
A18.03	1713	1886	1275	1093	1039	878
B19.01	1476	2076	1559	1073	993	963
B19.02	1803	2029	1100	1105	1087	1078
B19.03	1602	3237	1195	785	711	690
D21.01	1012	1066	749	738	651	672
D21.02	1466	972	787	830	747	787
D21.03	1290	2170	1155	738	661	547
E22.01	1682	2743	1531	1213	1141	1166
E22.02	1829	1403	1406	1299	1234	1216
E22.03	1706	3165	1336	1015	917	859
J24.01	2250	1029	857	822	686	662
J24.02	1555	1041	798	757	683	705
J24.03	1432	1659	1050	990	928	869
K25.01	2220	2001	1243	1221	1222	1256
K25.02	1742	2244	1334	1222	1206	1196
K25.03	1869	2213	1391	1426	1296	1343
M26.01	2034	1390	955	723	638	667
M26.02	1478	1283	908	651	688	700
M26.03	1793	1716	1015	998	1096	1083
P27.01	1498	1625	1174	1182	1226	1254
P27.02	1821	1927	1562	1565	1487	1340
P27.03	1488	1564	1195	1296	1282	1323
R28.01	1279	1135	662	656	588	633
R28.02	1256	717	599	567	567	550
R28.03	989	1244	768	752	756	737
Z29.01	1615	1268	934	890	837	831
Z29.02	1726	1650	1325	1172		1027
Z29.03	1014	1534	989	825	810	741
A30.01	1219	1253	794	805	892	829
A30.02	1095	1682	852	792	755	839
A30.03	1172	2059	935	811	756	679
B31.01	1877	1667	1241	1169	1066	1019
B31.02	1987	2452	1271	1172	1107	1051
B31.03	1927	1930	1180	1122	1109	1035
C32.01	1109	1199	706	735	716	683
C32.02	1133	1376	907	733	686	783
C32.03	1468	1622	870	778	739	732
D33.01	1485	981	930	951	904	1285
D33.02	1588	1805	1114	955	1031	985
D33.03	1672	1796	1207	1222	1185	1162
H34.01	1305	1334	1024	893	913	894
H34.02	1341	1392	853	815	867	904
H34.03	936	1658	926	752	788	825
J35.01	1362	1447	1138	1019	1091	1094
J35.02	1316	1480	1005	1046	934	917

$CD3^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
J35.03	1552	1411	1124	1069	977	989
K36.01	1418	1691	1067	1059	964	1083
K36.02	1151	1784	997	1054	1079	1141
K36.03	1295	2150	1226	1046	1084	1042
M37.01	0	1207	1027		979	948
M37.02	1305	882	804	767	784	779
M37.03	1165		703	642	663	625
O38.01	1197	1299	829	799	853	862
O38.02	1222	1363	730	724	751	840
O38.03	1379	1187	760	761	764	866

$CD4^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	769	522	456	502	449	461
B01-1.2	646	960	602	585	561	508
B01-1.3	753	707	516	548	541	585
E02-1.1	806	624	528	546	475	428
E02-1.2	929	1361	697	729	825	794
E02-1.3	933	691	803	807	790	740
Z03-1.1	738	786	607	461	504	497
Z03-1.2	559	634	435	436	315	430
Z03-1.3		902	582	493	494	446
G04-1.1	880	790	734	642	578	554
G04-1.2	654	743	624	651	612	632
G04-1.3	846	1191	719	616	601	532
P05-1.1	630	477	516	415	420	446
P05-1.2	784	1197	716	607	564	617
P05-1.3	696	684	641	619	619	621
P06-1.1	1306	1026	969	559	975	1038
P06-1.2	1350	1502	1217	1106	1137	1093
P06-1.3	1069	1275	788	666	733	698
G07-1.1	883	937	722	788	752	800
G07-1.2	842	986	869	751	798	871
G07-1.3	1019	982	795	768	843	924
R08-2.1	654	865	640	533	498	451
R08-2.2	731	773	542	448	435	407
R08-2.3	635	913	672	568	586	568
R09-2.1	655	812	592	497	507	445
R09-2.2	793	827	618	607	590	580
R09-2.3	851	958	849	700	645	591
W10-2.1	404	554	368	369	392	388
W10-2.2	445	466	324	327	318	333
W10-2.3	536	587	428	423	421	424
S11-3.1	902	976	631	691	666	767
S11-3.2	1024	736	682	713	671	
S11-3.3	763	667	646	721	642	693
T12-3.1	602	809	522	472	476	425

$CD4^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
T12-3.2	659	519	550	552	515	502
T12-3.3	824	572	595	572	541	468
C13-3.1	840	931	682	634	704	
C13-3.2	931	668	608	637		440
C13-3.3	1056	852	632	667	636	631
W14-3.1	761	625	619	504	352	
W14-3.2	832	1131	727	680	684	605
W14-3.3	877	847	724	628	575	503
X15-3.1	609	648	460	375	259	445
X15-3.2	819	787	509	469	453	426
X15-3.3	733	537	482	474	495	551
Y16-3.1	872	973	785	805	554	779
Y16-3.2	1159	1046	716	716	726	730
Y16-3.3	1322	1044	843	934	912	836
Z17-3.1	988	1061	337	752	692	682
Z17-3.2	1020	868		741	685	677
Z17-3.3	874	736	708	750	686	740
A18.01	1281	1186	920	862	867	811
A18.02	1303	956	824	919	848	874
A18.03	843	793	661	629	634	530
B19.01	788	919	705	599	617	592
B19.02	1017	926	631	693	653	637
B19.03	902	1346	651	520	482	444
D21.01	690	570	436	464	425	461
D21.02	947	608	514	533	491	510
D21.03	825	1123	656	480	464	378
E22.01	1004	915	711	691	623	667
E22.02	1016	658	624	617	680	685
E22.03	943	1047	630	568	562	533
J24.01	1437	584	563	536	462	425
J24.02	696	594	521	501	463	458
J24.03	879	759	608	586	559	551
K25.01	1107	834	626	660	643	675
K25.02	781	800	646	631	657	655
K25.03	1000	897	624	716	637	658
M26.01	1206	770	579	477	417	405
M26.02	894	684	548	431	473	443
M26.03	1078	944	621	665	685	681
P27.01	1017	1014	833	866	906	881
P27.02	1240	1328	1124	1125	1082	1033
P27.03	1049	981	826	880	852	917
R28.01	783	634	418	445	387	432
R28.02	734	428	375	377	386	366
R28.03	630	683	472	443	496	475
Z29.01	953	819	629	576	565	529
Z29.02	1035	981	795	716		658
Z29.03	626	807	586	531	520	489
A30.01	541	614	446	462	486	475
A30.02	576	718	439	452	428	449

$CD4^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
A30.03	638	836	509	451	428	376
B31.01	978	891	741	711	662	591
B31.02	1184	1289	814	759	719	652
B31.03	1039	1104	747	705	674	654
C32.01	704	676	493	497	479	467
C32.02	757	844	586	514	478	552
C32.03	965	935	575	526	506	502
D33.01	1014	669	656	644	627	801
D33.02	1149	1113	767	690	706	682
D33.03	1233	1117	867	858	800	840
H34.01	910	894	745	644	698	642
H34.02	935	982	651	579	624	659
H34.03	670	990	610	521	575	582
J35.01	999	1040	779	690	759	777
J35.02	935	971	715	746	678	640
J35.03	1091	893	750	760	685	683
K36.01	756	742	582	617	578	638
K36.02	716	733	562	620	655	706
K36.03	742	874	607	605	623	640
M37.01	0	707	609		582	550
M37.02	764	522	519	480	491	486
M37.03	731		417	408	448	415
O38.01	768	703	515	522	544	550
O38.02	767	725	446	489	513	574
O38.03	882	689	518	517	549	585

$CD8^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	631	524	422	422	403	410
B01-1.2	690	1430	632	531	451	442
B01-1.3	613	776	491	492	480	514
E02-1.1	563	520	300	258	201	233
E02-1.2	486	1200	446	382	448	453
E02-1.3	517	542	529	469	383	359
Z03-1.1	676	968	623	332	311	308
Z03-1.2	525	873	410	349	220	334
Z03-1.3		1035	528	404	354	325
G04-1.1	483	508	454	300	268	257
G04-1.2	308	447	381	322	341	317
G04-1.3	481	968	485	355	314	247
P05-1.1	569	545	482	411	387	389
P05-1.2	826	1737	917	724	568	575
P05-1.3	769	840	726	645	596	552
P06-1.1	851	715	650	345	574	652
P06-1.2	827	1073	774	656	647	670
P06-1.3	569	1119	515	401	446	408
G07-1.1	552	736	574	643	499	569

$CD8^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
G07-1.2	592	897	662	572	531	556
G07-1.3	729	878	605	503	493	610
R08-2.1	404	876	469	334	258	226
R08-2.2	458	790	413	267	241	218
R08-2.3	428	797	483	348	318	301
R09-2.1	479	903	468	344	328	293
R09-2.2	638	697	486	460	450	491
R09-2.3	664	1033	751	518	466	414
W10-2.1	214	353	190	196	184	188
W10-2.2	217	247	157	162	161	149
W10-2.3	247	342	217	180	211	176
S11-3.1	478	570	347	345	364	408
S11-3.2	573	460	388	402	378	
S11-3.3	399	392	350	394	357	385
T12-3.1	559	880	403	345	363	315
T12-3.2	493	451	433	418	409	352
T12-3.3	684	422	434	392	385	399
C13-3.1	454	760	351	327	408	
C13-3.2	523	498	346	327		236
C13-3.3	615	452	307	324	321	359
W14-3.1	497	624	572	406	235	
W14-3.2	516	1241	577	449	422	380
W14-3.3	486	541	397	349	317	306
X15-3.1	345	506	204	172	120	196
X15-3.2	482	573	223	185	188	198
X15-3.3	402	318	238	204	227	266
Y16-3.1	470	921	471	460	299	437
Y16-3.2	647	950	452	381	359	384
Y16-3.3	690	561	466	488	490	499
Z17-3.1	689	1236	291	611	516	525
Z17-3.2	837	1037		468	448	405
Z17-3.3	654	599	510	568	494	486
A18.01	1285	1794	1025	795	756	758
A18.02	1311	1122	828	820	797	827
A18.03	904	1122	632	464	437	356
B19.01	678	1074	756	441	377	367
B19.02	735	1002	416	397	400	404
B19.03	643	1712	472	256	243	249
D21.01	317	488	273	249	219	223
D21.02	489	331	262	277	230	267
D21.03	448	1008	460	209	192	163
E22.01	705	1753	808	527	482	523
E22.02	799	685	745	631	543	509
E22.03	721	2069	671	415	349	335
J24.01	820	448	276	268	207	228
J24.02	857	469	285	259	219	231
J24.03	526	880	460	381	361	304
K25.01	916	888	479	483	504	493
K25.02	893	1354	644	542	556	539

$CD8^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
K25.03	896	1269	678	703	633	618
M26.01	823	614	389	260	213	255
M26.02	641	566	354	212	244	289
M26.03	656	804	351	353	385	365
P27.01	496	594	335	316	337	355
P27.02	605	559	451	436	408	332
P27.03	469	568	399	382	382	412
R28.01	425	455	209	193	186	179
R28.02	427	281	199	202	199	183
R28.03	322	504	269	245	261	244
Z29.01	568	400	277	273	255	277
Z29.02	690	597	473	439		383
Z29.03	365	624	353	304	251	249
A30.01	601	616	339	358	407	344
A30.02	537	953	376	355	322	364
A30.03	570	1247	425	344	309	291
B31.01	837	682	492	459	407	408
B31.02	812	1054	454	409	392	394
B31.03	858	881	429	404	409	388
C32.01	361	463	224	239	219	214
C32.02	364	546	299	217	206	249
C32.03	506	660	290	231	220	232
D33.01	429	271	272	280	270	435
D33.02	421	677	309	251	288	273
D33.03	462	660	351	336	336	364
H34.01	370	380	266	234	219	234
H34.02	370	459	217	207	233	227
H34.03	251	654	297	205	211	218
J35.01	366	444	302	272	287	307
J35.02	354	451	271	277	244	239
J35.03	435	432	323	288	266	275
K36.01	598	960	502	392	345	393
K36.02	428	991	430	417	418	392
K36.03	521	1167	589	393	428	435
M37.01	0	458	394		407	383
M37.02	490	340	282	278	301	284
M37.03	423		261	224	227	212
O38.01	373	550	258	241	320	259
O38.02	397	555	279	191	199	225
O38.03	424	506	265	224	206	215

$CD19^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	228	129	144	116	138	120
B01-1.2	210	213	157	135	153	124
B01-1.3	195	113	152	135	134	145
E02-1.1	175	99	120	94	107	88
E02-1.2	210	240	204	176	170	151
E02-1.3	230	183	171	181	163	164
Z03-1.1	232	202	143	130	145	132
Z03-1.2	190	208	153	151	102	126
Z03-1.3		286	207	161	159	145
G04-1.1	326	259	215	187	159	184
G04-1.2	218	281	232	236	223	238
G04-1.3	259	321	211	201	208	168
P05-1.1	205	119	127	121	119	124
P05-1.2	206	259	208	218	137	146
P05-1.3	215	213	223	189	201	204
P06-1.1	420	318	270	291	296	334
P06-1.2	395	441	356	393	378	369
P06-1.3	319	466	268	245	217	233
G07-1.1	374	352	309	279	340	319
G07-1.2	339	365	330	322	384	349
G07-1.3	495	374	333	306	352	353
R08-2.1	247	396	218	191	164	159
R08-2.2	262	301	208	158	141	141
R08-2.3	250	413	229	234	186	203
R09-2.1	311	380	213	198	186	164
R09-2.2	359	368	326	317	271	317
R09-2.3	422	382	303	249	230	243
W10-2.1	141	219	130	147	153	180
W10-2.2	204	174	132	129	138	143
W10-2.3	210	203	124	149	128	148
S11-3.1	281	290	164	198	212	248
S11-3.2	310	213	222	279	267	
S11-3.3	218	171	207	219	222	234
T12-3.1	147	116	113	111	120	87
T12-3.2	142	105	129	116	100	108
T12-3.3	177	138	128	139	135	130
C13-3.1	170	200	140	135	160	
C13-3.2	165	146	140	133		78
C13-3.3	178	133	120	116	111	155
W14-3.1	541	282	396	247	218	
W14-3.2	526	694	408	389	349	345
W14-3.3	520	391	364	319	335	319
X15-3.1	250	241	162	150	78	145
X15-3.2	266	277	183	163	174	146
X15-3.3	211	174	163	152	178	213
Y16-3.1	442	373	268	291	161	283
Y16-3.2	357	365	300	243	231	229
Y16-3.3	485	345	323	305	334	287
Z17-3.1	343	329	119	260	220	258

$CD19^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	340	275		260	226	248
Z17-3.3	312	268	329	331	267	282
A18.01	465	378	271	283	274	260
A18.02	425	253	292	328	311	300
A18.03	170	166	168	176	156	131
B19.01	266	337	250	139	156	139
B19.02	272	250	187	170	183	178
B19.03	209	421	172	116	101	95
D21.01	464	449	351	300	280	269
D21.02	666	339	309	315	285	288
D21.03	553	464	323	284	252	219
E22.01	310	344	273	237	203	200
E22.02	279	210	208	202	176	205
E22.03	291	299	222	181	166	169
J24.01	494	172	173	178	150	142
J24.02	202	155	137	144	136	159
J24.03	252	194	151	120	132	139
K25.01	358	230	186	172	168	198
K25.02	237	231	166	160	162	184
K25.03	233	222	163	175	152	172
M26.01	463	234	175	156	148	183
M26.02	325	191	200	183	191	177
M26.03	393	256	195	204	246	247
P27.01	232	238	212	207	214	202
P27.02	321	401	343	384	312	279
P27.03	228	234	181	180	197	198
R28.01	493	353	246	231	237	249
R28.02	502	195	224	211	225	216
R28.03	377	305	240	269	265	310
Z29.01	428	274	224	233	229	241
Z29.02	369	273	282	308		272
Z29.03	245	274	193	200	203	188
A30.01	279	277	204	240	270	214
A30.02	284	320	201	203	207	254
A30.03	270	410	223	213	207	199
B31.01	416	345	259	238	257	255
B31.02	424	484	299	261	240	265
B31.03	422	420	244	242	248	247
C32.01	407	362	266	249	268	250
C32.02	446	441	326	278	269	325
C32.03	605	526	304	290	312	305
D33.01	351	211	188	208	183	235
D33.02	357	326	238	220	224	215
D33.03	439	360	262	325	321	314
H34.01	354	312	241	244	247	234
H34.02	521	424	253	293	335	345
H34.03	373	443	258	248	283	283
J35.01	376	344	301	295	327	295
J35.02	385	400	263	286	250	256

$CD19^+$ (cells/ul)	Baseline	IP	R15	R30	R45	R60
J35.03	407	387	316	315	278	261
K36.01	355	285	246	262	273	275
K36.02	298	310	234	238	242	303
K36.03	359	345	252	255	236	209
M37.01	0	284	246		257	235
M37.02	313	200	113	194	231	225
M37.03	229		160	174	170	156
O38.01	247	205	136	134	141	157
O38.02	214	178	183	118	136	163
O38.03	252	180	135	135	147	162

NK Cells (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	125	92	60	49	33	70
B01-1.2	120	548	107	62	78	83
B01-1.3	67	216	106	86	60	65
E02-1.1	316	288	120	102	64	98
E02-1.2	177	672	158	99	142	116
E02-1.3	167	316	185	135	81	96
Z03-1.1	530	1126	457	126	115	120
Z03-1.2	533	1185	312	262	224	238
Z03-1.3		1105	380	246	213	169
G04-1.1	150	302	128	79	72	75
G04-1.2	88	335	178	100	124	103
G04-1.3	149	590	177	72	69	63
P05-1.1	238	372	257	176	197	185
P05-1.2	351	1649	615	348	204	200
P05-1.3	434	537	406	309	221	217
P06-1.1	236	468	172	148	124	131
P06-1.2	202	858	212	166	136	105
P06-1.3	123	1250	303	141	106	103
G07-1.1	47	91	114	50	63	80
G07-1.2	73	145	73	38	42	52
G07-1.3	84	163	71	39	41	69
R08-2.1	375	1420	437	218	96	104
R08-2.2	162	1148	400	202	129	159
R08-2.3	291	1412	399	209	129	162
R09-2.1	113	833	151	101	62	65
R09-2.2	96	461	133	120	95	138
R09-2.3	216	902	421	121	78	78
W10-2.1	573	599	148	133	113	93
W10-2.2	264	489	138	84	83	141
W10-2.3	260	635	217	109	72	82
S11-3.1	103	317	79	64	79	80
S11-3.2	67	130	62	69	71	
S11-3.3	96	113	85	75	95	95
T12-3.1	164	644	110	47	44	57

NK Cells (cells/ul)	Baseline	IP	R15	R30	R45	R60
T12-3.2	55	145	109	65	61	91
T12-3.3	193	115	86	107	128	158
C13-3.1	186	483	64	66	168	
C13-3.2	185	224	125	109		97
C13-3.3	302	162	85	70	99	153
W14-3.1	78	258	121	41	56	
W14-3.2	60	622	103	73	78	96
W14-3.3	47	130	55	46	38	44
X15-3.1	299	489	111	133	61	95
X15-3.2	292	450	104	71	79	104
X15-3.3	150	225	131	89	103	148
Y16-3.1	199	973	200	130	104	238
Y16-3.2	266	1181	282	199	236	299
Y16-3.3	187	298	219	157	267	241
Z17-3.1	417	1576	192	256	259	204
Z17-3.2	476	1228		221	167	200
Z17-3.3	473	285	224	176	179	208
A18.01	139	510	223	103	72	87
A18.02	217	253	95	98	109	116
A18.03	179	347	128	70	82	57
B19.01	276	1032	717	187	97	128
B19.02	289	822	148	89	116	76
B19.03	224	2194	242	82	93	186
D21.01	134	658	158	88	95	100
D21.02	215	361	118	118	105	113
D21.03	173	1247	448	106	95	93
E22.01	50	379	76	28	25	37
E22.02	107	110	104	57	32	44
E22.03	76	558	84	52	34	44
J24.01	150	127	52	66	57	59
J24.02	414	209	92	87	81	104
J24.03	122	369	150	97	88	71
K25.01	250	582	150	84	113	121
K25.02	290	483	103	89	85	94
K25.03	98	481	133	142	117	122
M26.01	724	945	420	213	218	355
M26.02	513	713	256	78	140	326
M26.03	468	955	215	182	197	248
P27.01	604	739	192	188	164	173
P27.02	549	444	132	139	155	167
P27.03	306	843	183	210	239	187
R28.01	458	1089	159	102	94	117
R28.02	283	560	185	103	114	148
R28.03	143	1048	265	135	145	133
Z29.01	573	554	194	194	168	319
Z29.02	694	798	149	90		385
Z29.03	407	2051	582	174	151	130
A30.01	293	236	61	67	104	66
A30.02	136	694	79	50	41	50

NK Cells (cells/ul)	Baseline	IP	R15	R30	R45	R60
A30.03	196	1018	100	56	62	95
B31.01	297	278	110	80	90	116
B31.02	170	1042	90	60	65	93
B31.03	372	500	88	77	82	90
C32.01	278	702	109	127	144	146
C32.02	176	1068	241	112	80	137
C32.03	193	1356	171	73	73	132
D33.01	228	85	91	76	86	263
D33.02	84	598	127	50	54	63
D33.03	96	467	123	66	94	60
H34.01	97	155	65	47	54	60
H34.02	92	234	72	65	60	77
H34.03	64	775	161	76	71	62
J35.01	213	656	136	104	125	251
J35.02	156	988	148	132	133	145
J35.03	162	974	380	233	250	272
K36.01	268	461	106	116	90	100
K36.02	92	546	66	100	114	96
K36.03	106	734	109	97	110	86
M37.01	0	523	435		331	243
M37.02	241	462	88	130	103	143
M37.03	217		293	142	98	85
O38.01	135	740	112	109	238	166
O38.02	129	853	192	45	57	67
O38.03	338	385	71	53	57	90

$CD3^+$ (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	79	83	83	84	82	83
B01-1.2	78	76	82	83	82	82
B01-1.3	84	81	82	83	84	84
E02-1.1	72	74	80	79	79	75
E02-1.2	78	67	77	81	80	80
E02-1.3	78	72	75	78	82	79
Z03-1.1	64	58	67	76	77	75
Z03-1.2	61	54	66	68	67	67
Z03-1.3		57	66	67	69	72
G04-1.1	73	72	75	77	78	75
G04-1.2	75	67	72	74	75	74
G04-1.3	77	67	73	79	78	77
P05-1.1	74	65	73	75	73	72
P05-1.2	72	57	66	71	76	76
P05-1.3	69	67	69	71	76	74
P06-1.1	75	70	76	76	77	77
P06-1.2	76	68	77	76	77	77
P06-1.3	78	56	69	74	77	77
G07-1.1	78	79	77	79	78	79

$CD3^+$ (%)	Baseline	IP	R15	R30	R45	R60
G07-1.2	78	79	78	78	77	77
G07-1.3	76	78	78	78	78	78
R08-2.1	63	46	60	65	73	71
R08-2.2	72	50	61	66	69	65
R08-2.3	65	46	63	68	73	70
R09-2.1	72	57	72	72	74	74
R09-2.2	73	64	72	74	72	70
R09-2.3	70	60	68	75	78	77
W10-2.1	49	51	65	64	66	68
W10-2.2	60	50	64	68	67	63
W10-2.3	64	54	64	71	75	72
S11-3.1	78	72	76	79	78	78
S11-3.2	79	77	78	77	75	
S11-3.3	77	77	77	77	77	76
T12-3.1	76	62	78	83	81	82
T12-3.2	82	75	78	81	82	79
T12-3.3	78	78	79	77	76	73
C13-3.1	79	71	82	81	76	
C13-3.2	79	76	78	79		79
C13-3.3	77	80	81	82	80	75
W14-3.1	68	70	70	71	68	
W14-3.2	68	65	72	70	70	69
W14-3.3	70	73	70	72	69	69
X15-3.1	71	60	71	70	73	72
X15-3.2	70	62	71	73	72	72
X15-3.3	72	66	70	73	72	68
Y16-3.1	74	59	73	73	74	70
Y16-3.2	72	57	69	71	69	67
Y16-3.3	75	71	72	73	70	70
Z17-3.1	68	55	67	70	70	71
Z17-3.2	69	57		70	71	68
Z17-3.3	66	69	68	70	70	68
A18.01	80	77	80	80	81	81
A18.02	79	79	81	80	79	79
A18.03	81	77	80	81	80	81
B19.01	72	59	60	76	79	78
B19.02	75	65	76	80	77	81
B19.03	77	54	73	79	77	70
D21.01	62	48	60	64	64	64
D21.02	62	57	65	65	65	64
D21.03	63	54	59	64	63	62
E22.01	82	78	81	80	83	83
E22.02	81	81	81	82	84	82
E22.03	82	76	80	80	81	79
J24.01	77	76	79	77	77	76
J24.02	71	73	77	75	76	72
J24.03	78	73	77	80	79	79
K25.01	78	71	80	81	81	79
K25.02	76	75	83	84	81	80

$CD3^+$ (%)	Baseline	IP	R15	R30	R45	R60
K25.03	84	75	81	80	82	81
M26.01	63	54	62	66	63	55
M26.02	63	58	66	72	66	57
M26.03	68	59	71	71	72	68
P27.01	63	61	74	74	76	76
P27.02	67	68	75	74	75	75
P27.03	72	60	74	76	75	76
R28.01	56	43	61	65	63	63
R28.02	62	47	60	62	61	59
R28.03	65	47	58	64	63	63
Z29.01	61	60	68	67	67	59
Z29.02	61	60	74	74		59
Z29.03	58	40	54	68	69	69
A30.01	68	69	74	72	71	74
A30.02	71	61	75	75	74	73
A30.03	71	59	72	74	73	70
B31.01	72	71	75	76	74	72
B31.02	75	61	76	77	77	74
B31.03	70	66	77	77	76	74
C32.01	62	52	64	65	62	63
C32.02	64	45	61	65	64	62
C32.03	64	45	63	67	66	61
D33.01	71	76	77	77	76	71
D33.02	76	65	74	76	78	77
D33.03	75	67	74	76	74	75
H34.01	72	74	75	76	73	74
H34.02	68	67	70	69	68	67
H34.03	67	55	66	69	69	70
J35.01	69	58	72	72	70	65
J35.02	70	52	70	72	70	69
J35.03	72	51	61	65	64	63
K36.01	67	68	73	72	71	72
K36.02	71	68	76	75	72	73
K36.03	72	66	76	73	75	76
M37.01	0	58	58		63	65
M37.02	69	55	80	69	68	68
M37.03	71		59	67	70	70
O38.01	75	56	77	76	67	72
O38.02	76	56	64	81	80	77
O38.03	69	66	78	80	79	77

$CD4^+$ (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	41	40	41	44	42	42
B01-1.2	37	29	38	42	44	43
B01-1.3	44	37	41	42	43	43
E02-1.1	41	39	50	54	54	49
E02-1.2	51	35	46	53	52	50
E02-1.3	50	39	44	49	55	53
Z03-1.1	32	25	32	44	47	45
Z03-1.2	31	22	34	37	38	38
Z03-1.3		26	35	36	39	41
G04-1.1	46	42	45	51	52	51
G04-1.2	50	40	44	49	47	48
G04-1.3	48	36	42	49	50	52
P05-1.1	39	29	37	37	37	38
P05-1.2	35	23	28	32	37	39
P05-1.3	32	29	32	33	38	39
P06-1.1	44	40	44	46	47	46
P06-1.2	46	37	45	46	48	47
P06-1.3	50	28	40	44	47	48
G07-1.1	45	43	41	41	45	44
G07-1.2	45	40	43	42	45	45
G07-1.3	44	40	42	46	47	45
R08-2.1	38	22	34	40	48	49
R08-2.2	44	24	34	42	43	42
R08-2.3	38	24	35	42	47	45
R09-2.1	42	27	41	43	46	45
R09-2.2	40	34	40	42	41	38
R09-2.3	39	29	36	43	45	45
W10-2.1	30	30	42	41	45	46
W10-2.2	38	32	42	43	42	43
W10-2.3	42	33	41	48	48	49
S11-3.1	50	44	48	51	49	51
S11-3.2	49	46	49	49	47	
S11-3.3	49	47	49	49	48	48
T12-3.1	38	29	43	46	44	45
T12-3.2	45	39	43	45	45	45
T12-3.3	42	43	45	43	43	39
C13-3.1	48	38	52	52	45	
C13-3.2	49	43	47	50		49
C13-3.3	46	50	52	53	51	45
W14-3.1	40	33	36	39	40	
W14-3.2	41	30	38	41	42	41
W14-3.3	45	42	44	45	44	42
X15-3.1	44	32	49	48	51	49
X15-3.2	43	35	48	51	50	48
X15-3.3	45	40	47	49	48	46
Y16-3.1	48	29	44	46	47	45
Y16-3.2	45	29	42	46	44	43
Y16-3.3	49	45	46	47	45	42
Z17-3.1	39	24	34	37	40	39

$CD4^+$ (%)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	36	25		40	42	42
Z17-3.3	36	36	39	39	40	40
A18.01	39	31	37	41	43	41
A18.02	39	36	40	41	40	40
A18.03	38	32	41	47	48	47
B19.01	38	26	28	42	48	47
B19.02	41	29	44	49	47	49
B19.03	43	22	40	51	50	44
D21.01	42	26	36	41	43	43
D21.02	40	35	42	42	43	41
D21.03	39	28	34	43	43	41
E22.01	48	26	37	44	46	46
E22.02	44	39	36	39	45	47
E22.03	45	25	37	45	49	48
J24.01	49	42	52	51	53	49
J24.02	31	41	49	49	51	47
J24.03	47	33	43	47	47	50
K25.01	38	30	41	43	42	43
K25.02	34	27	40	44	43	43
K25.03	44	30	37	40	40	41
M26.01	37	31	37	43	41	34
M26.02	36	31	39	48	43	34
M26.03	42	33	45	47	46	44
P27.01	42	38	53	54	55	54
P27.02	45	47	54	53	54	57
P27.03	50	39	49	52	52	52
R28.01	34	24	39	44	42	44
R28.02	38	27	38	39	40	39
R28.03	42	26	35	39	41	41
Z29.01	36	38	46	44	45	37
Z29.02	35	36	44	45		36
Z29.03	35	21	32	43	45	45
A30.01	31	34	41	41	39	42
A30.02	36	26	40	41	42	40
A30.03	38	24	38	42	42	39
B31.01	38	39	44	45	45	42
B31.02	44	34	50	51	50	47
B31.03	38	37	49	49	48	46
C32.01	41	30	44	43	41	43
C32.02	44	26	40	46	44	42
C32.03	42	26	41	46	46	41
D33.01	49	52	54	53	52	44
D33.02	54	40	52	54	53	54
D33.03	54	41	51	54	51	52
H34.01	50	52	54	56	55	53
H34.02	48	46	52	50	50	49
H34.03	48	32	42	49	50	50
J35.01	50	39	50	50	49	46
J35.02	49	35	49	52	51	48

$CD4^+$ (%)	Baseline	IP	R15	R30	R45	R60
J35.03	50	34	42	46	45	44
K36.01	35	30	39	43	42	43
K36.02	42	29	43	45	42	45
K36.03	41	27	38	43	44	45
M37.01	0	34	34		37	37
M37.02	40	32	51	43	42	43
M37.03	44		35	43	46	45
O38.01	48	30	49	50	40	46
O38.02	48	30	39	56	56	53
O38.03	45	38	52	55	56	54

$CD8^+$ (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	34	40	38	37	37	37
B01-1.2	39	44	40	38	35	37
B01-1.3	36	41	39	38	38	38
E02-1.1	29	32	28	25	23	27
E02-1.2	27	31	29	28	28	28
E02-1.3	27	31	29	29	27	26
Z03-1.1	29	31	33	31	29	28
Z03-1.2	29	31	32	30	26	30
Z03-1.3		30	31	29	28	30
G04-1.1	25	27	28	24	24	24
G04-1.2	23	24	27	24	26	24
G04-1.3	27	29	28	28	26	24
P05-1.1	35	33	34	36	34	33
P05-1.2	36	33	36	38	37	36
P05-1.3	35	36	36	35	37	34
P06-1.1	29	28	29	29	28	29
P06-1.2	28	27	29	28	27	29
P06-1.3	26	25	26	27	29	28
G07-1.1	28	34	33	34	30	31
G07-1.2	31	36	32	32	30	29
G07-1.3	31	35	32	30	28	30
R08-2.1	23	22	25	25	25	24
R08-2.2	28	25	26	25	24	23
R08-2.3	26	21	25	26	25	24
R09-2.1	30	30	32	30	30	29
R09-2.2	32	29	32	32	31	32
R09-2.3	31	31	32	32	33	32
W10-2.1	16	19	22	22	21	22
W10-2.2	19	17	20	22	21	19
W10-2.3	19	19	21	21	24	21
S11-3.1	26	26	26	26	27	27
S11-3.2	27	29	28	27	26	
S11-3.3	25	28	27	27	27	27
T12-3.1	36	32	33	34	33	33

$CD8^+$ (%)	Baseline	IP	R15	R30	R45	R60
T12-3.2	34	34	34	34	36	31
T12-3.3	35	32	32	30	31	33
C13-3.1	26	31	27	27	26	
C13-3.2	28	32	27	26		27
C13-3.3	27	27	25	26	26	26
W14-3.1	26	33	33	31	27	
W14-3.2	25	33	31	27	26	25
W14-3.3	25	27	24	25	24	25
X15-3.1	25	25	22	22	23	21
X15-3.2	25	26	21	20	21	22
X15-3.3	25	24	23	21	22	22
Y16-3.1	26	27	27	26	25	25
Y16-3.2	25	26	27	25	22	23
Y16-3.3	25	24	25	24	24	25
Z17-3.1	27	28	30	30	30	30
Z17-3.2	30	29		26	27	25
Z17-3.3	27	29	28	30	29	26
A18.01	39	46	41	38	37	38
A18.02	40	42	40	37	38	38
A18.03	41	45	39	35	33	32
B19.01	33	30	30	31	29	29
B19.02	30	32	29	28	29	31
B19.03	30	28	29	25	25	24
D21.01	19	22	23	22	22	21
D21.02	21	19	22	22	20	22
D21.03	21	25	24	19	18	18
E22.01	34	49	42	33	35	36
E22.02	35	40	43	40	36	35
E22.03	35	49	40	33	31	30
J24.01	28	33	26	26	24	26
J24.02	39	32	27	25	24	24
J24.03	28	38	33	30	31	28
K25.01	32	32	31	31	33	31
K25.02	39	45	40	38	37	35
K25.03	39	43	40	39	40	39
M26.01	25	24	25	24	21	21
M26.02	26	26	25	24	22	22
M26.03	26	28	25	25	26	24
P27.01	20	22	21	20	21	22
P27.02	22	20	22	21	20	18
P27.03	22	22	24	23	23	23
R28.01	19	17	20	19	20	18
R28.02	22	18	20	21	21	19
R28.03	21	19	20	22	21	21
Z29.01	21	19	20	21	20	20
Z29.02	23	22	26	27		21
Z29.03	20	17	19	24	22	23
A30.01	34	34	31	32	33	30
A30.02	34	34	34	32	31	32

$CD8^+$ (%)	Baseline	IP	R15	R30	R45	R60
A30.03	34	35	32	32	30	30
B31.01	33	30	29	29	28	29
B31.02	30	27	28	27	27	28
B31.03	32	30	28	28	29	28
C32.01	21	21	20	21	19	19
C32.02	21	17	20	19	19	19
C32.03	22	19	21	20	20	19
D33.01	21	21	22	23	22	24
D33.02	20	24	21	20	22	22
D33.03	20	24	21	21	22	23
H34.01	20	22	19	20	17	19
H34.02	19	21	17	18	19	17
H34.03	18	21	21	19	18	19
J35.01	18	17	19	20	19	18
J35.02	19	16	19	19	18	18
J35.03	20	16	18	17	18	18
K36.01	28	38	34	27	25	26
K36.02	25	39	33	30	27	25
K36.03	29	36	36	28	30	31
M37.01	0	22	22		26	26
M37.02	26	21	28	25	26	25
M37.03	25		22	23	23	23
O38.01	23	23	25	23	24	22
O38.02	25	23	24	22	22	21
O38.03	22	28	26	24	21	20

$CD19^+$ (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	13	9	12	10	14	10
B01-1.2	13	6	10	11	12	10
B01-1.3	12	6	11	10	11	10
E02-1.1	9	6	10	10	12	10
E02-1.2	12	8	12	12	10	11
E02-1.3	11	10	11	11	12	12
Z03-1.1	11	6	8	12	13	12
Z03-1.2	10	7	11	12	10	12
Z03-1.3		9	12	12	13	13
G04-1.1	17	12	14	15	14	17
G04-1.2	17	15	15	18	16	17
G04-1.3	15	11	13	16	16	16
P05-1.1	12	8	9	10	10	11
P05-1.2	10	6	9	11	10	10
P05-1.3	10	9	11	10	12	13
P06-1.1	15	11	14	15	15	16
P06-1.2	15	10	14	16	16	17
P06-1.3	15	11	14	15	15	15
G07-1.1	19	16	16	17	18	17

$CD19^+$ (%)	Baseline	IP	R15	R30	R45	R60
G07-1.2	18	15	17	18	21	19
G07-1.3	21	15	17	19	19	18
R08-2.1	14	11	13	15	16	17
R08-2.2	17	10	13	14	15	15
R08-2.3	15	12	13	17	15	16
R09-2.1	20	13	15	17	18	17
R09-2.2	20	15	20	19	20	20
R09-2.3	19	12	13	16	16	17
W10-2.1	10	13	15	17	18	20
W10-2.2	17	13	17	18	18	18
W10-2.3	16	11	13	16	15	17
S11-3.1	16	13	15	15	15	16
S11-3.2	15	14	16	17	19	
S11-3.3	15	13	16	17	16	17
T12-3.1	10	6	9	10	12	10
T12-3.2	10	9	10	10	9	10
T12-3.3	9	11	10	11	10	11
C13-3.1	9	8	11	11	10	
C13-3.2	9	9	11	10		8
C13-3.3	8	8	10	10	9	11
W14-3.1	28	15	23	24	25	
W14-3.2	27	18	21	24	24	23
W14-3.3	26	20	24	24	27	26
X15-3.1	13	12	16	15	15	16
X15-3.2	13	13	18	18	19	15
X15-3.3	15	14	16	16	17	19
Y16-3.1	18	11	15	18	16	16
Y16-3.2	16	10	16	16	15	14
Y16-3.3	18	15	16	17	17	16
Z17-3.1	13	7	12	13	13	15
Z17-3.2	12	8		15	15	16
Z17-3.3	13	14	18	18	16	16
A18.01	15	9	10	13	14	13
A18.02	13	10	14	15	14	14
A18.03	8	7	11	13	12	12
B19.01	13	10	10	10	13	11
B19.02	11	8	13	12	13	13
B19.03	10	7	10	12	11	10
D21.01	29	20	27	26	27	26
D21.02	28	20	25	25	25	24
D21.03	27	12	17	24	25	26
E22.01	15	10	15	16	15	15
E22.02	13	12	12	13	12	14
E22.03	14	7	13	14	15	16
J24.01	17	13	16	16	17	16
J24.02	9	11	13	14	15	16
J24.03	14	9	11	10	11	13
K25.01	13	8	12	12	11	12
K25.02	10	8	10	11	11	13

$CD19^+$ (%)	Baseline	IP	R15	R30	R45	R60
K25.03	11	8	9	10	10	10
M26.01	14	9	11	14	15	15
M26.02	14	9	14	20	19	15
M26.03	14	9	13	15	16	15
P27.01	10	9	13	13	13	12
P27.02	12	14	17	18	16	16
P27.03	11	9	12	10	11	12
R28.01	22	14	23	23	25	24
R28.02	23	13	22	24	25	24
R28.03	24	12	19	22	23	26
Z29.01	16	13	16	17	18	17
Z29.02	13	10	16	20		16
Z29.03	15	7	11	17	17	18
A30.01	15	16	19	22	21	19
A30.02	19	12	17	20	21	22
A30.03	17	12	18	19	20	20
B31.01	16	14	16	16	18	18
B31.02	16	12	18	17	17	18
B31.03	15	15	16	16	17	18
C32.01	22	15	25	22	23	23
C32.02	25	15	21	24	26	26
C32.03	27	15	22	25	27	26
D33.01	17	16	16	17	16	13
D33.02	18	12	15	18	17	17
D33.03	20	14	17	20	20	21
H34.01	20	17	18	20	20	19
H34.02	26	21	22	24	26	25
H34.03	27	15	19	22	24	24
J35.01	19	14	19	20	21	18
J35.02	21	14	18	19	19	19
J35.03	19	13	17	19	18	17
K36.01	17	12	17	18	20	18
K36.02	20	11	18	17	17	19
K36.03	20	10	16	18	16	16
M37.01	0	14	14		16	16
M37.02	16	13	11	18	20	19
M37.03	14		13	18	18	18
O38.01	15	9	12	12	12	13
O38.02	13	7	16	13	14	15
O38.03	12	10	14	14	15	14

NK Cells (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	7	7	5	4	3	6
B01-1.2	7	17	7	5	6	7
B01-1.3	4	12	8	7	5	5
E02-1.1	17	18	10	10	7	11
E02-1.2	10	23	9	7	9	8
E02-1.3	8	17	12	9	6	7
Z03-1.1	24	34	24	11	10	11
Z03-1.2	28	38	23	21	21	22
Z03-1.3		34	22	19	17	15
G04-1.1	8	15	9	6	6	7
G04-1.2	7	17	12	7	9	8
G04-1.3	8	20	11	6	5	6
P05-1.1	14	26	18	14	17	17
P05-1.2	18	37	25	18	15	13
P05-1.3	20	23	19	17	13	13
P06-1.1	8	17	9	7	6	6
P06-1.2	8	20	8	7	6	5
P06-1.3	6	29	16	9	7	7
G07-1.1	2	4	6	3	3	4
G07-1.2	4	6	4	2	2	3
G07-1.3	4	7	4	2	2	3
R08-2.1	21	40	25	17	10	11
R08-2.2	10	38	24	18	13	17
R08-2.3	18	41	23	15	10	13
R09-2.1	7	28	11	9	6	7
R09-2.2	5	19	8	7	7	9
R09-2.3	10	27	18	8	6	5
W10-2.1	40	35	17	15	13	10
W10-2.2	22	36	18	12	11	18
W10-2.3	19	35	22	12	9	9
S11-3.1	6	14	7	5	5	5
S11-3.2	3	8	4	4	5	
S11-3.3	7	8	7	6	7	7
T12-3.1	11	31	9	4	4	6
T12-3.2	4	12	8	6	6	8
T12-3.3	10	9	7	8	10	13
C13-3.1	10	19	5	5	11	
C13-3.2	10	14	10	8		11
C13-3.3	13	10	7	6	8	11
W14-3.1	4	13	7	4	6	
W14-3.2	3	16	5	4	5	6
W14-3.3	2	7	4	3	3	4
X15-3.1	15	25	11	14	12	10
X15-3.2	15	22	10	8	8	11
X15-3.3	11	18	13	9	10	13
Y16-3.1	8	29	11	8	10	14
Y16-3.2	12	32	15	13	15	18
Y16-3.3	7	13	11	9	13	13
Z17-3.1	16	36	19	13	15	12

NK Cells (%)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	17	34		13	11	13
Z17-3.3	19	14	12	10	11	12
A18.01	4	12	9	5	4	4
A18.02	7	10	4	4	5	5
A18.03	9	15	8	5	7	5
B19.01	14	29	27	13	8	10
B19.02	12	26	10	7	8	6
B19.03	11	37	15	8	11	19
D21.01	8	30	12	8	9	10
D21.02	9	21	10	9	9	9
D21.03	9	32	23	9	9	11
E22.01	2	11	4	2	2	3
E22.02	5	6	6	4	2	3
E22.03	4	14	5	4	3	4
J24.01	5	10	5	6	6	7
J24.02	19	15	9	9	9	11
J24.03	7	16	11	8	8	7
K25.01	9	20	9	6	8	8
K25.02	13	16	6	6	6	6
K25.03	5	16	8	8	7	7
M26.01	22	36	27	19	21	29
M26.02	23	32	19	8	14	27
M26.03	17	33	15	13	13	15
P27.01	26	28	12	12	10	10
P27.02	20	16	6	7	8	9
P27.03	15	31	12	12	13	11
R28.01	20	42	15	10	10	11
R28.02	13	38	18	12	13	16
R28.03	9	40	21	11	12	11
Z29.01	22	26	14	14	13	23
Z29.02	25	29	8	6		23
Z29.03	24	52	32	15	13	12
A30.01	16	13	6	6	8	6
A30.02	9	25	7	5	4	4
A30.03	12	29	8	5	6	10
B31.01	11	11	7	5	6	8
B31.02	7	25	5	4	5	6
B31.03	13	17	6	5	5	6
C32.01	15	30	10	11	13	14
C32.02	10	37	16	10	8	11
C32.03	9	38	13	6	6	11
D33.01	11	6	8	6	7	15
D33.02	4	22	8	4	4	5
D33.03	4	18	8	4	6	4
H34.01	5	8	5	4	4	5
H34.02	5	12	6	5	5	6
H34.03	5	26	12	7	6	5
J35.01	11	27	8	7	8	15
J35.02	8	34	10	9	10	11

NK Cells (%)	Baseline	IP	R15	R30	R45	R60
J35.03	8	33	20	14	16	18
K36.01	13	19	7	8	7	7
K36.02	6	20	5	7	8	6
K36.03	6	22	7	7	7	6
M37.01	0	25	25		21	17
M37.02	13	29	9	12	9	12
M37.03	13		24	15	11	10
O38.01	8	33	10	10	20	14
O38.02	8	35	17	5	6	6
O38.03	17	22	8	5	6	8

Neutrophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	2773	2985	3006	3386	4581	5263
B01-1.2	3608	4535	3763	6118	7190	7746
B01-1.3	2793	3040	2436	2399	2579	3013
E02-1.1	5616	4457	5176	8486	9622	11063
E02-1.2	3954	6875	4209	4114	4643	5488
E02-1.3	3074	3294	3005	3293	3207	3711
Z03-1.1	1597	2077	1521	1360	1813	2808
Z03-1.2	3164	2941	2309	2744	2698	2567
Z03-1.3		1130	1323	1525	1338	1449
G04-1.1	3158	3622	3289	3279	3390	3769
G04-1.2	4221	5236	5713	5483	5263	5548
G04-1.3	4416	4787	3690	4616	4475	4371
P05-1.1	6670	6399	6019	6333	7282	8448
P05-1.2	3080	4087	2860	2906	3917	5150
P05-1.3	2230	3738	4284	4355	4821	5232
P06-1.1	2790	3649	3082	3120	3243	3599
P06-1.2	3686	4522	3619	3542	3908	3859
P06-1.3	3557	4202	2877	3091	3893	4854
G07-1.1	3541	3243	3033	2866	3306	3367
G07-1.2	2570	4025	3553	3509	3426	3648
G07-1.3	3213	3760	2921	2715	3040	3018
R08-2.1	4118	7188	6319	7930	8799	10210
R08-2.2	3283	4560	4215	4270	5767	8090
R08-2.3	2574	4253	3149	3637	4173	5495
R09-2.1	2012	5309	4644	5475	5860	5918
R09-2.2	3130		2077	2236	2253	2383
R09-2.3	2155	3067	2514	2296	2526	2981
W10-2.1	3311	3298	3365	4951	5663	6014
W10-2.2	2938	3010	2090	2084	2586	3314
W10-2.3	2754	3799	3062	3073	3281	3724
S11-3.1	5554	8248	6489	6734	6109	6461
S11-3.2	3634	5170	6072	6044	6355	-1
S11-3.3	5483	6689	6092	6175	6358	6737
T12-3.1	2197	4248	2875	2564	2979	2864
T12-3.2	2356	2693	2842	3116	3514	3475

Neutrophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
T12-3.3	2346	2140	2687	3244	3575	3881
C13-3.1	3738	5074	3578		5415	
C13-3.2	3203	3722	4668	5544	5649	
C13-3.3	3813	3714	3845	4532	6197	6457
W14-3.1	3369	4000	4082	2792		
W14-3.2	4046	6578	5121	5217	5641	6192
W14-3.3	2708	4079	3805	3898	4233	4998
X15-3.1	2894	4692	4929			8636
X15-3.2	2836	4459	4460	6806	7125	7553
X15-3.3	4111	4991	5159	6154	6961	7638
Y16-3.1	3251	5910	4830	5850	5852	7334
Y16-3.2	3317	4180	6006	6906	6769	7546
Y16-3.3	3162	3233	3599	4774	6459	7324
Z17-3.1	4960	8614	6880	7685	7837	8504
Z17-3.2	4259	7459		7632	8481	9185
Z17-3.3	7337	9943	10723	12175	11210	11588
A18.01	3478	3872	3125	2934	2921	3115
A18.02	2673	2582	2298	2239	2465	3227
A18.03	5152	9275	7960	7496	7834	7987
B19.01		8525	8845	8526	8270	9036
B19.02	3725	4811	3344	3530	4346	4755
B19.03	2519	5889	5944	8255	9031	10305
D21.01	8079	9765	7770	7516	7553	7461
D21.02	3892	3640	3185	3668	4015	4374
D21.03	3404	6743	5530	5285	6448	6964
E22.01	6179	9072	6768	7644	9606	9759
E22.02	4154	4920	4481	4920	5506	6466
E22.03	6374	9781	7480	8650	9736	11905
J24.01	3386	3845	4466	5670	6053	7673
J24.02	3294	3942	4182	5438	6656	8423
J24.03	3431	4377	3570	5062	4215	5799
K25.01	3629	7182	5862	5980	6322	6494
K25.02	3352	4283	4404	4984	5395	5520
K25.03	2736	3650	3431	4099	3631	4410
M26.01	1866	3373	3878	4408	5814	
M26.02	1994	2098	2677	3307	5258	7259
M26.03	1473	1853	1455	1870	1660	2954
P27.01	5538	7392	6312	7391	8603	9129
P27.02	5151	7403	7811	9039	10741	11106
P27.03	4856	6100	4946	5198	4988	5206
R28.01	2324	3462	3027	3719	4752	5445
R28.02	1804	2677	2993	3631	5247	6245
R28.03	1946	2825	2039	2246	1884	2472
Z29.01	4785	7242	7690	10071	11880	14112
Z29.02	4289	5292	4808	6840		
Z29.03	8619	12691	8940	8056	8567	8332
A30.01	2989	8514	7997	-1	7805	6930
A30.02	2552	5060	4877	5828	6286	6760
A30.03	2661	4150	3990	5623	6296	6336

Neutrophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
B31.01	3094	4614	5169	6312	7236	9145
B31.02	3367	5686	4240	5685	6995	7997
B31.03	3244	4688	4576	6396	8312	8953
C32.01	2424	3306	3966	3259	4272	4619
C32.02	2416	3816	2498	2554	2795	3092
C32.03	2407	4067	2705	2976	3264	3239
D33.01	4951	6384	5058	5860	7004	5838
D33.02	3358	4739	3381	3856	4792	5173
D33.03	4092	4964	3689	3882	4349	4498
H34.01	1474	2635	2861	3650	4342	4826
H34.02	1474	3004	3102	3864	4302	4602
H34.03	2331	5376	3898	3784	4621	4752
J35.01	3776	4836	4627	5867	6820	7323
J35.02	2846	4400	4723	5573	5843	6421
J35.03	2797	3976	3409	4410	5644	5783
K36.01	1909	6625	6855	8030	8692	9570
K36.02	3265	5535	4165	4719	4794	4963
K36.03	3364	4831	3788	5498	6785	7450
M37.01	4018	8812	9770		11219	11659
M37.02	3422	5145	5705	6703	7645	8270
M37.03	4342		6084	7387	8704	10448
O38.01	2115	5641	5062	5809	6560	6178
O38.02	2410	3495	2710	3485	4021	4392
O38.03	1922	2470	2220	3006	3555	3823

Monocytes (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	176	188	171	206	159	211
B01-1.2	255	230	202	160	229	230
B01-1.3	201	220	232	179	202	193
E02-1.1	912	655	547	707	787	832
E02-1.2	683	1425	721	683	625	744
E02-1.3	661	624	530	543	504	661
Z03-1.1	528	595	451	352	343	428
Z03-1.2	638	1132	698	730	677	704
Z03-1.3		605	445	380	390	360
G04-1.1	462	442	427	393	400	470
G04-1.2	479	585	578	540	621	608
G04-1.3	533	581	450	496	561	440
P05-1.1	563	675	713	731	688	816
P05-1.2	507	686	498	470	506	503
P05-1.3	436	488	490	536	561	533
P06-1.1	696	705	548	585	603	737
P06-1.2	745	896	718	684	735	698
P06-1.3	888	1071	516	484	567	718
G07-1.1	460	440	435	341	439	458
G07-1.2	403	569	539	583	504	554
G07-1.3	391	526	402	365	335	370

Monocytes (cells/ul)	Baseline	IP	R15	R30	R45	R60
R08-2.1	607	1041	579	545	473	536
R08-2.2	531	760	443	462	466	566
R08-2.3	478	845	493	445	428	517
R09-2.1	460	864	628	504	479	480
R09-2.2	459		417	344	383	437
R09-2.3	510	612	545	400	378	317
W10-2.1	308	465	250	302	368	421
W10-2.2	259	376	245	235	234	268
W10-2.3	294	391	288	248	268	396
S11-3.1	641	791	684	598	564	632
S11-3.2	711	1034	880	740	828	
S11-3.3	727	764	739	664	587	650
T12-3.1	374	754	322	276	275	297
T12-3.2	396	387	330	338	332	355
T12-3.3	449	400	392	418	508	465
C13-3.1	342	529	307		375	
C13-3.2	347	314	340	310	175	
C13-3.3	582	450	297	329	470	432
W14-3.1	413	288	391	200		
W14-3.2	490	809	439	474	577	506
W14-3.3	337	449	360	400	415	422
X15-3.1	345	488	298			374
X15-3.2	403	540	342	410	487	519
X15-3.3	502	546	469	553	616	703
Y16-3.1	470	614	359	374	354	409
Y16-3.2	446	563	496	338	348	490
Y16-3.3	333	464	433	432	422	388
Z17-3.1	837	1406	730	742	709	673
Z17-3.2	782	895		649	649	702
Z17-3.3	968	1072	952	1003	959	1080
A18.01	475	668	422	420	435	454
A18.02	502	409	367	368	426	413
A18.03	488	707	396	446	422	374
B19.01		638	520	504	440	480
B19.02	322	539	333	297	285	288
B19.03	383	871	240	359	498	583
D21.01	642	826	592	561	464	504
D21.02	400	348	300	286	286	354
D21.03	360	451	348	338	360	361
E22.01	664	1176	620	510	480	566
E22.02	442	412	396	393	385	448
E22.03	826	1271	660	519	513	644
J24.01	354	154	145	196	180	272
J24.02	403	288	191	330	370	364
J24.03	314	506	289	312	329	296
K25.01	552	609	442	371	385	425
K25.02	491	428	347	326	358	326
K25.03	382	475	371	342	319	326
M26.01	533	483	461	391	433	

Monocytes (cells/ul)	Baseline	IP	R15	R30	R45	R60
M26.02	434	278	281	302	400	534
M26.03	419	433	334	340	348	424
P27.01	464	550	361	407	377	464
P27.02	619	482	460	593	466	612
P27.03	520	879	360	485	466	479
R28.01	416	550	312	333	354	376
R28.02	444	391	378	309	429	501
R28.03	343	429	322	239	257	332
Z29.01	1009	857	850	1181	1166	1327
Z29.02	910	963	818	1058		
Z29.03	1241	2313	1392	1283	1079	1145
A30.01	535	770	666		605	512
A30.02	489	968	528	578	640	602
A30.03	480	916	456	497	521	624
B31.01	372	336	305	256	405	338
B31.02	403	618	296	353	445	421
B31.03	455	464	333	353	444	508
C32.01	461	586	391	394	486	446
C32.02	451	848	491	353	378	470
C32.03	383	780	400	386	379	441
D33.01	562	580	497	493	561	689
D33.02	394	722	360	347	436	462
D33.03	428	781	412	395	533	501
H34.01	460	403	340	302	342	365
H34.02	398	551	338	454	420	494
H34.03	491	1445	671	490	544	507
J35.01	291	385	297	262	308	338
J35.02	301	514	262	259	255	303
J35.03	302	348	348	314	370	362
K36.01	1210	631	458	500	530	510
K36.02	376	648	401	396	469	490
K36.03	464	810	478	518	581	682
M37.01	609	627	571		702	493
M37.02	415	413	370	403	437	470
M37.03	516		421	498	464	440
O38.01	396	590	363	407	428	379
O38.02	398	578	334	285	403	390
O38.03	423	499	289	288	342	424

Eosinophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	78	42	59	29	55	27
B01-1.2	41	74	45	30	44	18
B01-1.3	25	20	32	31	46	51
E02-1.1	129	101	92	73	46	52
E02-1.2	235	300	163	188	170	144
E02-1.3	218	168	148	185	170	118
Z03-1.1	101	56	37	32	25	23
Z03-1.2	51	84	54	54	42	37
Z03-1.3		40	25	23	24	21
G04-1.1	68	77	76	66	57	67
G04-1.2	120	69	85	67	73	76
G04-1.3	163	273	156	154	125	118
P05-1.1	88	117	107	119	84	95
P05-1.2	189	255	164	151	166	111
P05-1.3	78	59	77	47	57	44
P06-1.1	829	828	706	702	650	672
P06-1.2	729	711	616	554	540	482
P06-1.3	483	571	319	286	277	274
G07-1.1	221	205	174	160	189	183
G07-1.2	199	230	217	211	192	195
G07-1.3	233	234	176	165	173	207
R08-2.1	145	318	178	168	126	71
R08-2.2	845	1230	1020	823	719	515
R08-2.3	452	509	290	245	192	182
R09-2.1	142	163	138	117	84	53
R09-2.2	101		77	69	79	83
R09-2.3	125	68	66	39	44	48
W10-2.1	484	601	450	489	465	460
W10-2.2	446	472	326	313	285	273
W10-2.3	490	309	394	322	212	352
S11-3.1	187	142	90	110	91	80
S11-3.2	158	188	62	60	62	
S11-3.3	87	91	91	75	51	62
T12-3.1	105	123	74	48	45	52
T12-3.2	86	70	75	42	61	50
T12-3.3	133	76	95	71	54	62
C13-3.1	132	126	74		68	
C13-3.2	112	57	82	72	49	
C13-3.3	92	96	66	67	65	50
W14-3.1	77	58	44	28		
W14-3.2	75	103	69	59	55	50
W14-3.3	66	46	70	64	55	54
X15-3.1	106	74	50			40
X15-3.2	85	71	30	16	26	18
X15-3.3	124	84	67	95	70	48
Y16-3.1	67	89	69	94	31	48
Y16-3.2	62	53	67	53	35	58
Y16-3.3	96	61	43	65	62	58
Z17-3.1	573	740	500	456	480	353

Eosinophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	706	630		371	352	351
Z17-3.3	352	295	207	243	212	222
A18.01	79	134	93	67	77	65
A18.02	99	78	75	64	78	59
A18.03	112	74	59	37	29	29
B19.01		213	182	126	130	76
B19.02	261	183	135	106	99	96
B19.03	270	377	184	165	117	60
D21.01	150	90	97	64	64	54
D21.02	145	65	60	85	77	66
D21.03	128	154	87	69	32	67
E22.01	118	182	132	118	152	130
E22.02	117	99	73	76	74	66
E22.03	154	233	110	170	68	110
J24.01	95	22	23	28	23	10
J24.02	98	45	17	8	17	0
J24.03	137	150	106	85	79	99
K25.01	104	74	47	79	41	77
K25.02	50	53	13	20	37	89
K25.03	86	122	91	55	70	70
M26.01	852	585	480	378	350	
M26.02	490	307	299	202	193	156
M26.03	806	695	562	537	596	545
P27.01	301	286	189	194	178	128
P27.02	519	538	396	472	356	292
P27.03	448	394	302	270	296	281
R28.01	21	32	22	20	12	13
R28.02	22	18	13	5	7	15
R28.03	23	23	22	23	13	8
Z29.01	365	306	200	165	115	134
Z29.02	271	252	210	167		
Z29.03	116	130	84	64	76	53
A30.01	117	44	59		38	34
A30.02	103	88	53	45	41	34
A30.03	108	134	86	58	63	64
B31.01	124	110	121	64	63	44
B31.02	78	124	69	38	36	49
B31.03	124	96	58	41	51	32
C32.01	178	134	88	82	78	68
C32.02	71	96	50	37	30	44
C32.03	87	125	69	60	58	39
D33.01	193	143	145	162	116	193
D33.02	122	125	80	83	86	77
D33.03	104	118	87	71	98	91
H34.01	156	86	129	94	89	45
H34.02	168	157	94	90	72	72
H34.03	185	307	183	165	141	117
J35.01	186	208	191	162	167	160
J35.02	112	126	83	94	75	82

Eosinophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
J35.03	130	163	137	122	85	100
K36.01	189	107	70	80	42	70
K36.02	95	99	59	66	68	70
K36.03	87	62	71	53	70	67
M37.01	315	239	190		122	151
M37.02	262	233	185	160	177	140
M37.03	208		117	116	113	83
O38.01	383	352	158	126	134	103
O38.02	446	449	268	235	218	238
O38.03	578	437	255	252	189	209

Basophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
B01-1.1	15	5	14	20	6	20
B01-1.2	23	16	17	8	18	37
B01-1.3	20	20	12	12	21	28
E02-1.1	43	50	50	42	0	0
E02-1.2	55	50	48	47	57	72
E02-1.3	35	42	32	50	32	47
Z03-1.1	26	25	25	22	21	23
Z03-1.2	23	30	32	34	19	32
Z03-1.3		30	25	20	21	21
G04-1.1	34	26	11	26	26	22
G04-1.2	19	39	23	15	22	23
G04-1.3	28	44	30	27	40	25
P05-1.1	18	27	16	34	28	0
P05-1.2	24	20	0	17	6	30
P05-1.3	10	13	14	34	21	22
P06-1.1	37	16	46	39	34	51
P06-1.2	32	52	55	43	30	29
P06-1.3	43	82	35	33	32	37
G07-1.1	25	31	17	28	24	24
G07-1.2	26	22	12	6	24	13
G07-1.3	25	22	28	10	22	22
R08-2.1	33	64	53	69	53	12
R08-2.2	45	50	30	27	0	20
R08-2.3	36	38	46	23	43	38
R09-2.1	26	29	35	29	46	38
R09-2.2	0		30	22	31	18
R09-2.3	30	34	44	34	13	29
W10-2.1	28	50	25	40	30	39
W10-2.2	5	27	14	10	16	9
W10-2.3	25	19	24	28	33	28
S11-3.1	62	24	36	28	33	62
S11-3.2	0	0	26	43	53	
S11-3.3	32	36	42	33	26	18
T12-3.1	17	66	41	28	14	17
T12-3.2	22	44	22	33	36	30

Basophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
T12-3.3	26	36	41	26	16	39
C13-3.1	18	34	27		30	
C13-3.2	11	23	13	29	28	
C13-3.3	36	30	39	18	32	17
W14-3.1	24	38	32	20		
W14-3.2	41	80	31	15	47	58
W14-3.3	31	53	29	29	31	27
X15-3.1	27	22	12			20
X15-3.2	11	36	18	8	17	18
X15-3.3	19	21	13	24	44	29
Y16-3.1	24	20	28	16	23	38
Y16-3.2	31	26	34	36	26	29
Y16-3.3	26	18	18	36	26	29
Z17-3.1	55	104	50	42	109	46
Z17-3.2	60	76		72	55	12
Z17-3.3	66	67	83	30	85	89
A18.01	29	36	25	22	28	24
A18.02	20	22	24	20	16	18
A18.03	24	62	20	28	29	10
B19.01		25	36	21	20	11
B19.02	20	104	26	27	12	19
B19.03	20	26	24	0	11	36
D21.01	21	26	49	18	9	0
D21.02	14	24	35	16	11	12
D21.03	31	33	16	35	16	8
E22.01	18	42	19	10	0	12
E22.02	21	21	13	14	15	8
E22.03	38	47	20	0	11	0
J24.01	41	6	12	14	30	19
J24.02	24	38	46	53	52	20
J24.03	23	32	41	71	18	46
K25.01	14	21	24	16	16	9
K25.02	32	15	19	27	15	15
K25.03	29	29	23	6	17	32
M26.01	39	34	32	25	15	
M26.02	36	29	32	24	21	28
M26.03	21	51	23	33	44	39
P27.01	17	22	17	10	22	23
P27.02	46	34	32	48	14	14
P27.03	24	30	14	15	30	23
R28.01	16	19	18	5	6	0
R28.02	18	23	13	20	0	0
R28.03	12	17	19	15	13	20
Z29.01	26	10	20	25	0	0
Z29.02	16	18	8	29		
Z29.03	35	56	36	42	33	0
A30.01	27	44	0		29	25
A30.02	19	18	20	30	16	26
A30.03	29	42	29	29	32	24

Basophils (cells/ul)	Baseline	IP	R15	R30	R45	R60
B31.01	25	29	14	24	27	22
B31.02	20	41	19	23	27	39
B31.03	26	32	32	33	20	43
C32.01	29	31	33	10	30	12
C32.02	28	32	18	12	22	29
C32.03	31	25	32	28	38	34
D33.01	39	59	28	31	45	42
D33.02	41	42	27	33	13	35
D33.03	35	42	46	35	33	26
H34.01	20	34	18	26	24	13
H34.02	12	17	14	22	18	20
H34.03	25	30	31	17	38	39
J35.01	19	23	33	23	18	19
J35.02	15	24	13	22	15	16
J35.03	16	21	17	13	15	31
K36.01	0	68	26	40	21	35
K36.02	21	36	12	20	41	21
K36.03	29	35	18	30	44	58
M37.01	42	80	12		41	14
M37.02	24	38	37	34	28	10
M37.03	54		39	9	10	12
O38.01	45	53	40	44	42	47
O38.02	43	41	26	60	45	37
O38.03	33	52	37	32	56	39

Neutrophils (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	56.6	63.5	66.8	69.1	75.1	77.4
B01-1.2	62.2	55.3	67.2	80.5	81.7	84.2
B01-1.3	57	60.8	60.9	61.5	61.4	65.5
E02-1.1	65.3	61.9	72.9	81.6	84.4	85.1
E02-1.2	57.3	55	61.9	61.4	65.4	68.6
E02-1.3	52.1	54.9	56.7	58.8	60.5	62.9
Z03-1.1	36.3	33.5	37.1	42.5	51.8	62.4
Z03-1.2	55.5	38.7	51.3	56	57.4	55.8
Z03-1.3		22.6	37.8	46.2	44.6	48.3
G04-1.1	55.4	56.6	60.9	64.3	65.2	67.3
G04-1.2	67	68	74.2	74.1	72.1	73
G04-1.3	62.2	54.4	61.5	68.9	67.8	70.5
P05-1.1	75.8	71.1	73.4	74.5	78.3	79.7
P05-1.2	52.2	41.7	45.4	51.9	61.2	69.6
P05-1.3	45.5	57.5	61.2	65	67.9	70.7
P06-1.1	37.7	44.5	46.7	48	48.4	49.3
P06-1.2	45.5	43.9	46.4	49.2	52.1	53.6
P06-1.3	50.1	41.2	49.6	56.2	61.8	65.6
G07-1.1	56.2	52.3	52.3	52.1	54.2	55.2
G07-1.2	50.4	55.9	57.3	56.6	57.1	57.9
G07-1.3	51	51.5	53.1	54.3	56.3	53.9

Neutrophils (%)	Baseline	IP	R15	R30	R45	R60
R08-2.1	62.4	56.6	71	80.1	83.8	85.8
R08-2.2	51.3	45.6	56.2	62.8	73	80.1
R08-2.3	49.5	44.3	54.3	63.8	67.3	72.3
R09-2.1	46.8	55.3	67.3	75	77.1	78.9
R09-2.2	55.9		48.3	52	51.2	51.8
R09-2.3	43.1	45.1	45.7	53.4	57.4	62.1
W10-2.1	60.2	53.2	67.3	73.9	75.5	77.1
W10-2.2	61.2	56.8	59.7	61.3	66.3	70.5
W10-2.3	56.2	60.3	63.8	66.8	69.8	67.7
S11-3.1	62.4	69.9	72.1	73.2	73.6	72.6
S11-3.2	46	55	69	71.1	71.4	
S11-3.3	69.4	73.5	73.4	74.4	74.8	75.7
T12-3.1	52.3	51.8	62.5	64.1	66.2	66.6
T12-3.2	54.8	61.2	64.6	66.3	68.9	69.5
T12-3.3	46	53.5	59.7	63.6	66.2	69.3
C13-3.1	62.3	60.4	67.5		72.2	
C13-3.2	57.2	65.3	74.1	77	80.7	
C13-3.3	53.7	61.9	69.9	74.3	76.5	77.8
W14-3.1	57.1	62.5	64.8	69.8		
W14-3.2	59.5	57.7	66.5	70.5	71.4	74.6
W14-3.3	53.1	61.8	65.6	67.2	69.4	73.5
X15-3.1	54.6	63.4	79.5			85.5
X15-3.2	53.5	62.8	75.6	83	81.9	83
X15-3.3	66.3	71.3	77	77.9	79.1	80.4
Y16-3.1	53.3	59.7	70	75	76	77.2
Y16-3.2	53.5	47.5	71.5	77.6	77.8	78.6
Y16-3.3	49.4	53	59	66.3	73.4	75.5
Z17-3.1	54.5	58.2	68.8	72.5	71.9	74.6
Z17-3.2	50.1	59.2		74.1	77.1	78.5
Z17-3.3	66.7	74.2	77.7	80.1	79.5	78.3
A18.01	48.3	43.5	50.4	52.4	53.1	52.8
A18.02	40.5	46.1	48.9	45.7	47.4	54.7
A18.03	64.4	74.8	80.4	80.6	81.6	83.2
B19.01	.	68.2	73.1	81.2	82.7	82.9
B19.02	55.6	55.3	64.3	66.6	70.1	74.3
B19.03	49.4	45.3	74.3	85.1	85.2	86.6
D21.01	75.5	75.7	80.1	81.7	83	82.9
D21.02	56.4	61.7	63.7	69.2	73	72.9
D21.03	55.8	61.3	70	76.6	80.6	82.9
E22.01	67.9	64.8	72	78	82.1	82.7
E22.02	60.2	69.3	67.9	71.3	74.4	77.9
E22.03	66.4	63.1	74.8	81.6	85.4	86.9
J24.01	49.8	69.9	77	81	80.7	79.1
J24.02	54	61.6	72.1	72.5	77.4	83.4
J24.03	60.2	55.4	60.5	71.3	69.1	76.3
K25.01	52.6	68.4	74.2	75.7	77.1	76.4
K25.02	53.2	57.1	69.9	73.3	73.9	74.6
K25.03	48	50.7	60.2	67.2	62.6	68.9
M26.01	28.7	49.6	60.6	71.1	76.5	

Neutrophils (%)	Baseline	IP	R15	R30	R45	R60
M26.02	39.1	43.7	58.2	68.9	76.2	78.9
M26.03	27.8	32.5	38.3	45.6	41.5	53.7
P27.01	64.4	67.2	73.4	76.2	77.5	78.7
P27.02	56.6	66.1	73	74.7	78.4	79.9
P27.03	60.7	60.4	68.7	67.5	67.4	68.5
R28.01	44.7	54.1	68.8	75.9	77.9	82.5
R28.02	41	58.2	69.6	74.1	79.5	81.1
R28.03	49.9	48.7	55.1	59.1	57.1	61.8
Z29.01	55	71	76.9	79.3	82.5	84
Z29.02	52.3	58.8	64.1	69.8		
Z29.03	74.3	68.6	74.5	76	78.6	78.6
A30.01	56.4	77.4	81.6		81.3	82.5
A30.02	54.3	57.5	73.9	77.7	77.6	78.6
A30.03	54.3	49.4	70	78.1	79.7	79.2
B31.01	49.9	63.2	72.8	78.9	80.4	83.9
B31.02	51.8	55.2	67.3	75.8	78.6	81.6
B31.03	49.9	58.6	71.5	78	82.3	82.9
C32.01	50.5	54.2	72.1	67.9	71.2	74.5
C32.02	51.4	47.7	55.5	62.3	65	63.1
C32.03	47.2	49	58.8	64.7	68	66.1
D33.01	64.3	76	73.3	76.1	78.7	69.5
D33.02	57.9	57.1	63.8	70.1	72.6	73.9
D33.03	59.3	59.1	63.6	65.8	66.9	69.2
H34.01	37.8	54.9	62.2	70.2	73.6	75.4
H34.02	37.8	51.8	66	69	71.7	70.8
H34.03	55.5	54.3	63.9	68.8	72.2	73.1
J35.01	60.9	62.8	70.1	76.2	77.5	77.9
J35.02	55.8	55.7	73.8	77.4	77.9	78.3
J35.03	51.8	56	59.8	68.9	73.3	75.1
K36.01	30.3	68.3	77.9	80.3	82	82.5
K36.02	61.6	61.5	70.6	71.5	70.5	70.9
K36.03	58	54.9	64.2	73.3	77.1	77.6
M37.01	57.4	77.3	82.1		83.1	85.1
M37.02	56.1	68.6	77.1	79.8	82.2	82.7
M37.03	64.8		78	83	84.5	87.8
O38.01	47	64.1	76.7	78.5	78.1	78.2
O38.02	50.2	51.4	61.6	69.7	71.8	72
O38.03	40.9	47.5	60	66.8	69.7	69.5

Monocytes (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	3.6	4	3.8	4.2	2.6	3.1
B01-1.2	4.4	2.8	3.6	2.1	2.6	2.5
B01-1.3	4.1	4.4	5.8	4.6	4.8	4.2
E02-1.1	10.6	9.1	7.7	6.8	6.9	6.4
E02-1.2	9.9	11.4	10.6	10.2	8.8	9.3
E02-1.3	11.2	10.4	10	9.7	9.5	11.2
Z03-1.1	12	9.6	11	11	9.8	9.5
Z03-1.2	11.2	14.9	15.5	14.9	14.4	15.3
Z03-1.3		12.1	12.7	11.5	13	12
G04-1.1	8.1	6.9	7.9	7.7	7.7	8.4
G04-1.2	7.6	7.6	7.5	7.3	8.5	8
G04-1.3	7.5	6.6	7.5	7.4	8.5	7.1
P05-1.1	6.4	7.5	8.7	8.6	7.4	7.7
P05-1.2	8.6	7	7.9	8.4	7.9	6.8
P05-1.3	8.9	7.5	7	8	7.9	7.2
P06-1.1	9.4	8.6	8.3	9	9	10.1
P06-1.2	9.2	8.7	9.2	9.5	9.8	9.7
P06-1.3	12.5	10.5	8.9	8.8	9	9.7
G07-1.1	7.3	7.1	7.5	6.2	7.2	7.5
G07-1.2	7.9	7.9	8.7	9.4	8.4	8.8
G07-1.3	6.2	7.2	7.3	7.3	6.2	6.6
R08-2.1	9.2	8.2	6.5	5.5	4.5	4.5
R08-2.2	8.3	7.6	5.9	6.8	5.9	5.6
R08-2.3	9.2	8.8	8.5	7.8	6.9	6.8
R09-2.1	10.7	9	9.1	6.9	6.3	6.4
R09-2.2	8.2		9.7	8	8.7	9.5
R09-2.3	10.2	9	9.9	9.3	8.6	6.6
W10-2.1	5.6	7.5	5	4.5	4.9	5.4
W10-2.2	5.4	7.1	7	6.9	6	5.7
W10-2.3	6	6.2	6	5.4	5.7	7.2
S11-3.1	7.2	6.7	7.6	6.5	6.8	7.1
S11-3.2	9	11	10	8.7	9.3	
S11-3.3	9.2	8.4	8.9	8	6.9	7.3
T12-3.1	8.9	9.2	7	6.9	6.1	6.9
T12-3.2	9.2	8.8	7.5	7.2	6.5	7.1
T12-3.3	8.8	10	8.7	8.2	9.4	8.3
C13-3.1	5.7	6.3	5.8		5	
C13-3.2	6.2	5.5	5.4	4.3	2.5	
C13-3.3	8.2	7.5	5.4	5.4	5.8	5.2
W14-3.1	7	4.5	6.2	5		
W14-3.2	7.2	7.1	5.7	6.4	7.3	6.1
W14-3.3	6.6	6.8	6.2	6.9	6.8	6.2
X15-3.1	6.5	6.6	4.8			3.7
X15-3.2	7.6	7.6	5.8	5	5.6	5.7
X15-3.3	8.1	7.8	7	7	7	7.4
Y16-3.1	7.7	6.2	5.2	4.8	4.6	4.3
Y16-3.2	7.2	6.4	5.9	3.8	4	5.1
Y16-3.3	5.2	7.6	7.1	6	4.8	4
Z17-3.1	9.2	9.5	7.3	7	6.5	5.9

Monocytes (%)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	9.2	7.1		6.3	5.9	6
Z17-3.3	8.8	8	6.9	6.6	6.8	7.3
A18.01	6.6	7.5	6.8	7.5	7.9	7.7
A18.02	7.6	7.3	7.8	7.5	8.2	7
A18.03	6.1	5.7	4	4.8	4.4	3.9
B19.01		5.1	4.3	4.8	4.4	4.4
B19.02	4.8	6.2	6.4	5.6	4.6	4.5
B19.03	7.5	6.7	3	3.7	4.7	4.9
D21.01	6	6.4	6.1	6.1	5.1	5.6
D21.02	5.8	5.9	6	5.4	5.2	5.9
D21.03	5.9	4.1	4.4	4.9	4.5	4.3
E22.01	7.3	8.4	6.6	5.2	4.1	4.8
E22.02	6.4	5.8	6	5.7	5.2	5.4
E22.03	8.6	8.2	6.6	4.9	4.5	4.7
J24.01	5.2	2.8	2.5	2.8	2.4	2.8
J24.02	6.6	4.5	3.3	4.4	4.3	3.6
J24.03	5.5	6.4	4.9	4.4	5.4	3.9
K25.01	8	5.8	5.6	4.7	4.7	5
K25.02	7.8	5.7	5.5	4.8	4.9	4.4
K25.03	6.7	6.6	6.5	5.6	5.5	5.1
M26.01	8.2	7.1	7.2	6.3	5.7	
M26.02	8.5	5.8	6.1	6.3	5.8	5.8
M26.03	7.9	7.6	8.8	8.3	8.7	7.7
P27.01	5.4	5	4.2	4.2	3.4	4
P27.02	6.8	4.3	4.3	4.9	3.4	4.4
P27.03	6.5	8.7	5	6.3	6.3	6.3
R28.01	8	8.6	7.1	6.8	5.8	5.7
R28.02	10.1	8.5	8.8	6.3	6.5	6.5
R28.03	8.8	7.4	8.7	6.3	7.8	8.3
Z29.01	11.6	8.4	8.5	9.3	8.1	7.9
Z29.02	11.1	10.7	10.9	10.8		
Z29.03	10.7	12.5	11.6	12.1	9.9	10.8
A30.01	10.1	7	6.8		6.3	6.1
A30.02	10.4	11	8	7.7	7.9	7
A30.03	9.8	10.9	8	6.9	6.6	7.8
B31.01	6	4.6	4.3	3.2	4.5	3.1
B31.02	6.2	6	4.7	4.7	5	4.3
B31.03	7	5.8	5.2	4.3	4.4	4.7
C32.01	9.6	9.6	7.1	8.2	8.1	7.2
C32.02	9.6	10.6	10.9	8.6	8.8	9.6
C32.03	7.5	9.4	8.7	8.4	7.9	9
D33.01	7.3	6.9	7.2	6.4	6.3	8.2
D33.02	6.8	8.7	6.8	6.3	6.6	6.6
D33.03	6.2	9.3	7.1	6.7	8.2	7.7
H34.01	11.8	8.4	7.4	5.8	5.8	5.7
H34.02	10.2	9.5	7.2	8.1	7	7.6
H34.03	11.7	14.6	11	8.9	8.5	7.8
J35.01	4.7	5	4.5	3.4	3.5	3.6
J35.02	5.9	6.5	4.1	3.6	3.4	3.7

Monocytes (%)	Baseline	IP	R15	R30	R45	R60
J35.03	5.6	4.9	6.1	4.9	4.8	4.7
K36.01	19.2	6.5	5.2	5	5	4.4
K36.02	7.1	7.2	6.8	6	6.9	7
K36.03	8	9.2	8.1	6.9	6.6	7.1
M37.01	8.7	5.5	4.8		5.2	3.6
M37.02	6.8	5.5	5	4.8	4.7	4.7
M37.03	7.7		5.4	5.6	4.5	3.7
O38.01	8.8	6.7	5.5	5.5	5.1	4.8
O38.02	8.3	8.5	7.6	5.7	7.2	6.4
O38.03	9	9.6	7.8	6.4	6.7	7.7

Eosinophils (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	1.6	0.9	1.3	0.6	0.9	0.4
B01-1.2	0.7	0.9	0.8	0.4	0.5	0.2
B01-1.3	0.5	0.4	0.8	0.8	1.1	1.1
E02-1.1	1.5	1.4	1.3	0.7	0.4	0.4
E02-1.2	3.4	2.4	2.4	2.8	2.4	1.8
E02-1.3	3.7	2.8	2.8	3.3	3.2	2
Z03-1.1	2.3	0.9	0.9	1	0.7	0.5
Z03-1.2	0.9	1.1	1.2	1.1	0.9	0.8
Z03-1.3		0.8	0.7	0.7	0.8	0.7
G04-1.1	1.2	1.2	1.4	1.3	1.1	1.2
G04-1.2	1.9	0.9	1.1	0.9	1	1
G04-1.3	2.3	3.1	2.6	2.3	1.9	1.9
P05-1.1	1	1.3	1.3	1.4	0.9	0.9
P05-1.2	3.2	2.6	2.6	2.7	2.6	1.5
P05-1.3	1.6	0.9	1.1	0.7	0.8	0.6
P06-1.1	11.2	10.1	10.7	10.8	9.7	9.2
P06-1.2	9	6.9	7.9	7.7	7.2	6.7
P06-1.3	6.8	5.6	5.5	5.2	4.4	3.7
G07-1.1	3.5	3.3	3	2.9	3.1	3
G07-1.2	3.9	3.2	3.5	3.4	3.2	3.1
G07-1.3	3.7	3.2	3.2	3.3	3.2	3.7
R08-2.1	2.2	2.5	2	1.7	1.2	0.6
R08-2.2	13.2	12.3	13.6	12.1	9.1	5.1
R08-2.3	8.7	5.3	5	4.3	3.1	2.4
R09-2.1	3.3	1.7	2	1.6	1.1	0.7
R09-2.2	1.8		1.8	1.6	1.8	1.8
R09-2.3	2.5	1	1.2	0.9	1	1
W10-2.1	8.8	9.7	9	7.3	6.2	5.9
W10-2.2	9.3	8.9	9.3	9.2	7.3	5.8
W10-2.3	10	4.9	8.2	7	4.5	6.4
S11-3.1	2.1	1.2	1	1.2	1.1	0.9
S11-3.2	2	2	0.7	0.7	0.7	
S11-3.3	1.1	1	1.1	0.9	0.6	0.7
T12-3.1	2.5	1.5	1.6	1.2	1	1.2
T12-3.2	2	1.6	1.7	0.9	1.2	1

Eosinophils (%)	Baseline	IP	R15	R30	R45	R60
T12-3.3	2.6	1.9	2.1	1.4	1	1.1
C13-3.1	2.2	1.5	1.4		0.9	
C13-3.2	2	1	1.3	1	0.7	
C13-3.3	1.3	1.6	1.2	1.1	0.8	0.6
W14-3.1	1.3	0.9	0.7	0.7		
W14-3.2	1.1	0.9	0.9	0.8	0.7	0.6
W14-3.3	1.3	0.7	1.2	1.1	0.9	0.8
X15-3.1	2	1	0.8			0.4
X15-3.2	1.6	1	0.5	0.2	0.3	0.2
X15-3.3	2	1.2	1	1.2	0.8	0.5
Y16-3.1	1.1	0.9	1	1.2	0.4	0.5
Y16-3.2	1	0.6	0.8	0.6	0.4	0.6
Y16-3.3	1.5	1	0.7	0.9	0.7	0.6
Z17-3.1	6.3	5	5	4.3	4.4	3.1
Z17-3.2	8.3	5		3.6	3.2	3
Z17-3.3	3.2	2.2	1.5	1.6	1.5	1.5
A18.01	1.1	1.5	1.5	1.2	1.4	1.1
A18.02	1.5	1.4	1.6	1.3	1.5	1
A18.03	1.4	0.6	0.6	0.4	0.3	0.3
B19.01		1.7	1.5	1.2	1.3	0.7
B19.02	3.9	2.1	2.6	2	1.6	1.5
B19.03	5.3	2.9	2.3	1.7	1.1	0.5
D21.01	1.4	0.7	1	0.7	0.7	0.6
D21.02	2.1	1.1	1.2	1.6	1.4	1.1
D21.03	2.1	1.4	1.1	1	0.4	0.8
E22.01	1.3	1.3	1.4	1.2	1.3	1.1
E22.02	1.7	1.4	1.1	1.1	1	0.8
E22.03	1.6	1.5	1.1	1.6	0.6	0.8
J24.01	1.4	0.4	0.4	0.4	0.3	0.1
J24.02	1.6	0.7	0.3	0.1	0.2	0
J24.03	2.4	1.9	1.8	1.2	1.3	1.3
K25.01	1.5	0.7	0.6	1	0.5	0.9
K25.02	0.8	0.7	0.2	0.3	0.5	1.2
K25.03	1.5	1.7	1.6	0.9	1.2	1.1
M26.01	13.1	8.6	7.5	6.1	4.6	
M26.02	9.6	6.4	6.5	4.2	2.8	1.7
M26.03	15.2	12.2	14.8	13.1	14.9	9.9
P27.01	3.5	2.6	2.2	2	1.6	1.1
P27.02	5.7	4.8	3.7	3.9	2.6	2.1
P27.03	5.6	3.9	4.2	3.5	4	3.7
R28.01	0.4	0.5	0.5	0.4	0.2	0.2
R28.02	0.5	0.4	0.3	0.1	0.1	0.2
R28.03	0.6	0.4	0.6	0.6	0.4	0.2
Z29.01	4.2	3	2	1.3	0.8	0.8
Z29.02	3.3	2.8	2.8	1.7		
Z29.03	1	0.7	0.7	0.6	0.7	0.5
A30.01	2.2	0.4	0.6		0.4	0.4
A30.02	2.2	1	0.8	0.6	0.5	0.4
A30.03	2.2	1.6	1.5	0.8	0.8	0.8

Eosinophils (%)	Baseline	IP	R15	R30	R45	R60
B31.01	2	1.5	1.7	0.8	0.7	0.4
B31.02	1.2	1.2	1.1	0.5	0.4	0.5
B31.03	1.9	1.2	0.9	0.5	0.5	0.3
C32.01	3.7	2.2	1.6	1.7	1.3	1.1
C32.02	1.5	1.2	1.1	0.9	0.7	0.9
C32.03	1.7	1.5	1.5	1.3	1.2	0.8
D33.01	2.5	1.7	2.1	2.1	1.3	2.3
D33.02	2.1	1.5	1.5	1.5	1.3	1.1
D33.03	1.5	1.4	1.5	1.2	1.5	1.4
H34.01	4	1.8	2.8	1.8	1.5	0.7
H34.02	4.3	2.7	2	1.6	1.2	1.1
H34.03	4.4	3.1	3	3	2.2	1.8
J35.01	3	2.7	2.9	2.1	1.9	1.7
J35.02	2.2	1.6	1.3	1.3	1	1
J35.03	2.4	2.3	2.4	1.9	1.1	1.3
K36.01	3	1.1	0.8	0.8	0.4	0.6
K36.02	1.8	1.1	1	1	1	1
K36.03	1.5	0.7	1.2	0.7	0.8	0.7
M37.01	4.5	2.1	1.6		0.9	1.1
M37.02	4.3	3.1	2.5	1.9	1.9	1.4
M37.03	3.1		1.5	1.3	1.1	0.7
O38.01	8.5	4	2.4	1.7	1.6	1.3
O38.02	9.3	6.6	6.1	4.7	3.9	3.9
O38.03	12.3	8.4	6.9	5.6	3.7	3.8

Basophils (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	0.3	0.1	0.3	0.4	0.1	0.3
B01-1.2	0.4	0.2	0.3	0.1	0.2	0.4
B01-1.3	0.4	0.4	0.3	0.3	0.5	0.6
E02-1.1	0.5	0.7	0.7	0.4	0	0
E02-1.2	0.8	0.4	0.7	0.7	0.8	0.9
E02-1.3	0.6	0.7	0.6	0.9	0.6	0.8
Z03-1.1	0.6	0.4	0.6	0.7	0.6	0.5
Z03-1.2	0.4	0.4	0.7	0.7	0.4	0.7
Z03-1.3		0.6	0.7	0.6	0.7	0.7
G04-1.1	0.6	0.4	0.2	0.5	0.5	0.4
G04-1.2	0.3	0.5	0.3	0.2	0.3	0.3
G04-1.3	0.4	0.5	0.5	0.4	0.6	0.4
P05-1.1	0.2	0.3	0.2	0.4	0.3	0
P05-1.2	0.4	0.2	0	0.3	0.1	0.4
P05-1.3	0.2	0.2	0.2	0.5	0.3	0.3
P06-1.1	0.5	0.2	0.7	0.6	0.5	0.7
P06-1.2	0.4	0.5	0.7	0.6	0.4	0.4
P06-1.3	0.6	0.8	0.6	0.6	0.5	0.5
G07-1.1	0.4	0.5	0.3	0.5	0.4	0.4
G07-1.2	0.5	0.3	0.2	0.1	0.4	0.2
G07-1.3	0.4	0.3	0.5	0.2	0.4	0.4

Basophils (%)	Baseline	IP	R15	R30	R45	R60
R08-2.1	0.5	0.5	0.6	0.7	0.5	0.1
R08-2.2	0.7	0.5	0.4	0.4	0	0.2
R08-2.3	0.7	0.4	0.8	0.4	0.7	0.5
R09-2.1	0.6	0.3	0.5	0.4	0.6	0.5
R09-2.2	0		0.7	0.5	0.7	0.4
R09-2.3	0.6	0.5	0.8	0.8	0.3	0.6
W10-2.1	0.5	0.8	0.5	0.6	0.4	0.5
W10-2.2	0.1	0.5	0.4	0.3	0.4	0.2
W10-2.3	0.5	0.3	0.5	0.6	0.7	0.5
S11-3.1	0.7	0.2	0.4	0.3	0.4	0.7
S11-3.2	0	0	0.3	0.5	0.6	
S11-3.3	0.4	0.4	0.5	0.4	0.3	0.2
T12-3.1	0.4	0.8	0.9	0.7	0.3	0.4
T12-3.2	0.5	1	0.5	0.7	0.7	0.6
T12-3.3	0.5	0.9	0.9	0.5	0.3	0.7
C13-3.1	0.3	0.4	0.5		0.4	
C13-3.2	0.2	0.4	0.2	0.4	0.4	
C13-3.3	0.5	0.5	0.7	0.3	0.4	0.2
W14-3.1	0.4	0.6	0.5	0.5		
W14-3.2	0.6	0.7	0.4	0.2	0.6	0.7
W14-3.3	0.6	0.8	0.5	0.5	0.5	0.4
X15-3.1	0.5	0.3	0.2			0.2
X15-3.2	0.2	0.5	0.3	0.1	0.2	0.2
X15-3.3	0.3	0.3	0.2	0.3	0.5	0.3
Y16-3.1	0.4	0.2	0.4	0.2	0.3	0.4
Y16-3.2	0.5	0.3	0.4	0.4	0.3	0.3
Y16-3.3	0.4	0.3	0.3	0.5	0.3	0.3
Z17-3.1	0.6	0.7	0.5	0.4	1	0.4
Z17-3.2	0.7	0.6		0.7	0.5	0.1
Z17-3.3	0.6	0.5	0.6	0.2	0.6	0.6
A18.01	0.4	0.4	0.4	0.4	0.5	0.4
A18.02	0.3	0.4	0.5	0.4	0.3	0.3
A18.03	0.3	0.5	0.2	0.3	0.3	0.1
B19.01		0.2	0.3	0.2	0.2	0.1
B19.02	0.3	1.2	0.5	0.5	0.2	0.3
B19.03	0.4	0.2	0.3	0	0.1	0.3
D21.01	0.2	0.2	0.5	0.2	0.1	0
D21.02	0.2	0.4	0.7	0.3	0.2	0.2
D21.03	0.5	0.3	0.2	0.5	0.2	0.1
E22.01	0.2	0.3	0.2	0.1	0	0.1
E22.02	0.3	0.3	0.2	0.2	0.2	0.1
E22.03	0.4	0.3	0.2	0	0.1	0
J24.01	0.6	0.1	0.2	0.2	0.4	0.2
J24.02	0.4	0.6	0.8	0.7	0.6	0.2
J24.03	0.4	0.4	0.7	1	0.3	0.6
K25.01	0.2	0.2	0.3	0.2	0.2	0.1
K25.02	0.5	0.2	0.3	0.4	0.2	0.2
K25.03	0.5	0.4	0.4	0.1	0.3	0.5
M26.01	0.6	0.5	0.5	0.4	0.2	

Basophils (%)	Baseline	IP	R15	R30	R45	R60
M26.02	0.7	0.6	0.7	0.5	0.3	0.3
M26.03	0.4	0.9	0.6	0.8	1.1	0.7
P27.01	0.2	0.2	0.2	0.1	0.2	0.2
P27.02	0.5	0.3	0.3	0.4	0.1	0.1
P27.03	0.3	0.3	0.2	0.2	0.4	0.3
R28.01	0.3	0.3	0.4	0.1	0.1	0
R28.02	0.4	0.5	0.3	0.4	0	0
R28.03	0.3	0.3	0.5	0.4	0.4	0.5
Z29.01	0.3	0.1	0.2	0.2	0	0
Z29.02	0.2	0.2	0.1	0.3		
Z29.03	0.3	0.3	0.3	0.4	0.3	0
A30.01	0.5	0.4	0		0.3	0.3
A30.02	0.4	0.2	0.3	0.4	0.2	0.3
A30.03	0.6	0.5	0.5	0.4	0.4	0.3
B31.01	0.4	0.4	0.2	0.3	0.3	0.2
B31.02	0.3	0.4	0.3	0.3	0.3	0.4
B31.03	0.4	0.4	0.5	0.4	0.2	0.4
C32.01	0.6	0.5	0.6	0.2	0.5	0.2
C32.02	0.6	0.4	0.4	0.3	0.5	0.6
C32.03	0.6	0.3	0.7	0.6	0.8	0.7
D33.01	0.5	0.7	0.4	0.4	0.5	0.5
D33.02	0.7	0.5	0.5	0.6	0.2	0.5
D33.03	0.5	0.5	0.8	0.6	0.5	0.4
H34.01	0.5	0.7	0.4	0.5	0.4	0.2
H34.02	0.3	0.3	0.3	0.4	0.3	0.3
H34.03	0.6	0.3	0.5	0.3	0.6	0.6
J35.01	0.3	0.3	0.5	0.3	0.2	0.2
J35.02	0.3	0.3	0.2	0.3	0.2	0.2
J35.03	0.3	0.3	0.3	0.2	0.2	0.4
K36.01	0	0.7	0.3	0.4	0.2	0.3
K36.02	0.4	0.4	0.2	0.3	0.6	0.3
K36.03	0.5	0.4	0.3	0.4	0.5	0.6
M37.01	0.6	0.7	0.1		0.3	0.1
M37.02	0.4	0.5	0.5	0.4	0.3	0.1
M37.03	0.8		0.5	0.1	0.1	0.1
O38.01	1	0.6	0.6	0.6	0.5	0.6
O38.02	0.9	0.6	0.6	1.2	0.8	0.6
O38.03	0.7	1	1	0.7	1.1	0.7

IgG (mg/dl)	Baseline	IP	R15	R30	R45	R60
B01-1.1	685	725	678	673	664	685
B01-1.2	678	731	685	677	689	670
B01-1.3	656	726	675	648	656	656
E02-1.1	952	1037	1000	973	955	986
E02-1.2	1000	1088	1023	992	953	998
E02-1.3	984	1006	967	934	899	921
Z03-1.1	1323	1362	1318	1281	1278	1341
Z03-1.2	1272	1361	1306	1234	1312	1240
Z03-1.3	1267	1328	1252	1210	1231	1234
G04-1.1	1040	1124	1105	1034	1050	1048
G04-1.2	1069	1094	1055	1012	1009	1032
G04-1.3	1091	1261	1131	1085	1014	1017
P05-1.1	1151	1096	1077	1069	1080	1083
P05-1.2	1124	1300	1175	1573	1114	1143
P05-1.3	1195	1166	1145	1172	1122	1119
P06-1.1	1105	1107	1118	1069	1146	1129
P06-1.2	1099	1153	1088	1076	1061	1064
P06-1.3	1029	1349	951	992	978	970
G07-1.1	949	929	916	926	965	981
G07-1.2	971	1044	966	941	983	997
G07-1.3	911	989	926	929	875	910
R08-2.1	1287	1347	1281	1249	1244	1275
R08-2.2	1163	1359	1289	1233	1242	1264
R08-2.3	1222	1380	1252	1249	1228	1258
R09-2.1	1230	1318	1281	1244	1190	1179
R09-2.2	1169	1336	1187	1160	1175	1175
R09-2.3	1294	1436	1368	1325	1267	1255
W10-2.1	1477	1561	1406	1441	1418	1423
W10-2.2	1365	1543	1387	1298	1355	1317
W10-2.3	1445	1557	1474	1398	1430	1309
S11-3.1	663	745	662	626	630	640
S11-3.2	568	568	548	521	529	
S11-3.3	655	684	626	607	624	624
T12-3.1	1166	1276	1130	1086	1112	1066
T12-3.2	1005	1124	1149	1018	1049	1069
T12-3.3	1175	1169	1163	1152	1149	1160
C13-3.1	1169	1279	1109	1074	1254	1228
C13-3.2	1107	1107	979	1066	927	950
C13-3.3	1265	1202	1064	1067	1122	1235
W14-3.1	1052	1091	1100	1030	1075	1103
W14-3.2	945	1105	1010	971	976	914
W14-3.3	1093	1096	1025	1027	1073	1117
X15-3.1	1086	1181	1061	991	1010	1016
X15-3.2	994	1053	937	1029	1016	968
X15-3.3	1050	1090	1025	1033	1005	1027
Y16-3.1	973	1058	1016	986	939	994
Y16-3.2	989	1067	955	1016	1032	1029
Y16-3.3	1105	1140	1082	1175	1158	1244
Z17-3.1	1260	1326	1240	1270	1279	1240

IgG (mg/dl)	Baseline	IP	R15	R30	R45	R60
Z17-3.2	1138	1155	1102	1086	1099	1154
Z17-3.3	1338	1323	1302	1354	1336	1388
A18.01	1150	1159	1100	1091	1085	1074
A18.02	1041	1088	1011	968	989	976
A18.03	1032	1076	998	966	1004	972
B19.01	967	1080	986	986	981	953
B19.02	1038	1060	976	931	910	918
B19.03	910	938	894	883	858	855
D21.01	1094	1210	1103	1037	1080	1031
D21.02	1169	1227	1107	1099	1093	1088
D21.03	1151	1258	1163	1118	1118	1127
E22.01	1123	1225	1115	1077	1071	1141
E22.02	1141	1209	1195	1138	1141	1149
E22.03	1076	1279	1205	1130	1142	1190
J24.01	1046	1104	1038	1068	1033	1052
J24.02	1073	1097	995	1001	1053	1079
J24.03	988	1059	1011	938	938	915
K25.01	934	973	866	848	851	846
K25.02	834	902	778	780	770	796
K25.03	820	851	764	751	766	743
M26.01	1215	1235	1178	1158	1144	1189
M26.02	1218	1248	1172	1142	1199	1142
M26.03	1071	1131	1110	1035	1011	1144
P27.01	1429	1399	1315	1297	1312	1353
P27.02	1314	1393	1289	1298	1298	1304
P27.03	1250	1343	1292	1234	1253	1244
R28.01	1121	1172	1082	1038	1038	1038
R28.02	1106	1118	1091	1065	1065	1085
R28.03	1011	1077	1011	985	1002	1014
Z29.01	1181	1169	1127	1158	1167	1161
Z29.02	1151	1124	1056	1130		1160
Z29.03	1113	1153	1068	1014	1095	1080
A30.01	1619	1643	1484	1558	1795	1546
A30.02	1757	1789	1643	1640	1643	1666
A30.03	1618	1775	1634	1600	1655	1575
B31.01	940	953	856	868	886	873
B31.02	938	1022	945	889	883	895
B31.03	936	954	871	843	864	846
C32.01	1200	1117	1106	1109	1187	1171
C32.02	1317	1429	1348	1299	1276	1333
C32.03	1227	1374	1255	1227	1207	1272
D33.01	808	791	761	808	810	905
D33.02	784	844	768	751	736	724
D33.03	759	811	755	735	726	738
H34.01	1046	1066	1074	1033	1025	1051
H34.02	1152	1253	1087	1051	1056	1072
H34.03	1047	1218	1123	1090	1058	1060
J35.01	779	873	775	765	756	775
J35.02	775	861	825	796	750	746

IgG (mg/dl)	Baseline	IP	R15	R30	R45	R60
J35.03	718	801	762	721	738	750
K36.01	1061	1127	1046	1046	1014	1030
K36.02	1007	1228	1018	971	974	1026
K36.03	1034	1148	970	954	988	1017
M37.01	1520	1537	1446		1637	1579
M37.02	1385	1616	1443	1368	1380	1431
M37.03	1398		1424	1359	1316	1316
O38.01	1187	1146	1168	1154	1217	1160
O38.02	1171	1331	1219	1173	1179	1231
O38.03	1107	1241	1143	1154	1140	1145
R39.01	1168	1207	1187	1162	1151	1085

IgM (mg/dl)	Baseline	IP	R15	R30	R45	R60
B01-1.1	203	211	197	200	194	201
B01-1.2	189	197	180	179	192	178
B01-1.3	188	204	190	185	184	191
E02-1.1	51	50	51	48	52	50
E02-1.2	49	47	45	44	45	46
E02-1.3	38	41	40	44	36	37
Z03-1.1	123	122	115	116	115	114
Z03-1.2	111	114	107	103	107	112
Z03-1.3	102	110	104	98	104	100
G04-1.1	93	94	87	87	85	82
G04-1.2	84	87	82	77	79	78
G04-1.3	102	107	94	93	93	103
P05-1.1	168	159	159	156	163	157
P05-1.2	167	182	162	164	153	156
P05-1.3	169	164	162	165	164	157
P06-1.1	127	126	116	115	130	126
P06-1.2	125	128	119	117	117	117
P06-1.3	117	126	105	109	104	102
G07-1.1	143	139	140	138	140	140
G07-1.2	143	147	140	135	139	151
G07-1.3	140	139	133	127	122	126
R08-2.1	115	117	109	107	106	106
R08-2.2	103	114	109	106	103	106
R08-2.3	92	103	96	94	89	92
R09-2.1	105	105	104	101	100	95
R09-2.2	96	107	95	96	94	94
R09-2.3	122	136	131	121	118	119
W10-2.1	170	175	164	163	162	163
W10-2.2	162	176	156	152	148	147
W10-2.3	169	172	164	158	155	143
S11-3.1	39	46	37	38	37	37
S11-3.2	30	30	28	22	28	
S11-3.3	57	66	61	63	60	60

IgM (mg/dl)	Baseline	IP	R15	R30	R45	R60
T12-3.1	194	216	196	181	184	179
T12-3.2	178	194	202	170	188	183
T12-3.3	197	190	185	187	186	186
C13-3.1	116	124	110	106	122	117
C13-3.2	113	108	99	106	91	92
C13-3.3	123	115	103	98	103	124
W14-3.1	71	73	74	67	70	75
W14-3.2	62	71	62	62	62	62
W14-3.3	79	83	75	74	79	81
X15-3.1	72	80	67	64	66	66
X15-3.2	59	62	60	62	60	59
X15-3.3	64	66	65	60	61	63
Y16-3.1	89	127	120	115	113	113
Y16-3.2	114	118	104	114	117	117
Y16-3.3	118	115	113	122	124	125
Z17-3.1	208	230	206	207	210	199
Z17-3.2	182	180	172	174	167	180
Z17-3.3	196	190	190	191	199	201
A18.01	75	81	74	70	66	75
A18.02	62	67	56	58	58	58
A18.03	60	56	56	51	55	58
B19.01	67	72	68	67	64	66
B19.02	76	74	68	68	65	66
B19.03	80	79	72	72	71	74
D21.01	40	44	39	40	40	40
D21.02	41	41	37	37	38	38
D21.03	38	41	38	37	35	36
E22.01	95	104	94	86	89	95
E22.02	93	88	88	87	85	88
E22.03	76	85	79	76	73	79
J24.01	146	152	141	141	143	143
J24.02	145	143	128	132	138	139
J24.03	134	148	138	131	128	129
K25.01	82	84	77	75	74	75
K25.02	71	75	64	65	64	66
K25.03	68	69	67	57	62	60
M26.01	112	113	107	105	106	109
M26.02	115	116	108	107	114	111
M26.03	101	111	105	95	97	106
P27.01	204	203	185	191	191	196
P27.02	206	216	193	196	204	199
P27.03	186	197	187	182	187	187
R28.01	101	102	96	84	94	94
R28.02	100	97	93	92	94	94
R28.03	91	97	89	88	87	86
Z29.01	65	62	63	64	65	63
Z29.02	70	70	63	66		70
Z29.03	70	75	70	63	74	65
A30.01	181	171	158	166	190	165

IgM (mg/dl)	Baseline	IP	R15	R30	R45	R60
A30.02	188	184	171	166	169	178
A30.03	175	188	182	173	180	170
B31.01	74	74	67	68	67	69
B31.02	73	77	71	69	66	69
B31.03	73	76	67	66	68	64
C32.01	131	119	118	116	121	121
C32.02	147	158	146	138	138	144
C32.03	132	146	137	132	131	133
D33.01	90	84	83	84	86	95
D33.02	88	95	89	86	83	84
D33.03	83	92	83	82	82	80
H34.01	103	101	96	92	92	95
H34.02	108	114	103	99	95	98
H34.03	102	112	109	105	99	99
J35.01	118	130	120	115	113	121
J35.02	114	130	123	114	117	116
J35.03	112	123	115	109	110	111
K36.01	128	131	121	123	116	121
K36.02	116	136	111	110	108	113
K36.03	117	133	113	108	118	117
M37.01	101	102	94		108	104
M37.02	84	96	85	83	83	83
M37.03	95		92	91	88	87
O38.01	214	201	208	205	214	206
O38.02	206	234	208	206	206	204
O38.03	195	208	190	194	195	196

Oxidative Burst (%)	Baseline	IP	R15	R30	R45	R60
B01-1.1	100	99	97	98	94	99
B01-1.2	99	97	98	99	100	99
B01-1.3	96	95	96	95	96	96
E02-1.1	99	98	98	100	100	100
E02-1.2	99	98	96	95	95	97
E02-1.3	95	98	96	99	94	99
Z03-1.1	93	96	97	97	98	97
Z03-1.2	97	95	95	95	96	95
Z03-1.3		93	94	90	92	94
G04-1.1	97	71	93	100	97	97
G04-1.2	94	98	99	99	97	97
G04-1.3	98	98	98	97	98	98
P05-1.1	99	100	100	100	97	97
P05-1.2	99	97	99	99	99	99
P05-1.3	97	100	100	99	100	100
P06-1.1	100	97	97	98	99	99
P06-1.2	96	99	99	99	99	98
P06-1.3	99	98	99	99	99	99

Oxidative Burst (%)	Baseline	IP	R15	R30	R45	R60
G07-1.1	99	98	99	98	98	96
G07-1.2	95	98	98	98	99	99
G07-1.3	98	98	98	98	98	98
R08-2.1	100	100	99	100	100	100
R08-2.2	90	99	99	99	99	100
R08-2.3	100	97	97	98	98	99
R09-2.1	99	100	99	100	100	100
R09-2.2	92	83	85	85	90	93
R09-2.3	94	94	91	89	87	92
W10-2.1	100	100	99	100	100	100
W10-2.2	93	97	93	95	98	96
W10-2.3	98	98	96	96	97	96
S11-3.1	95	96	97	98	97	97
S11-3.2	96	97	92	95	96	
S11-3.3	93	91	92	87	86	95
T12-3.1	93	96	97	96	97	97
T12-3.2	98	99	94	98	97	97
T12-3.3	94	92	96	98	98	97
C13-3.1	95	93	94	95	96	77
C13-3.2	96	98	94	92		
C13-3.3	97	90	93	98	98	95
W14-3.1	94	93	93	95	76	
W14-3.2	96	97	95	94	95	94
W14-3.3	94	96	97	98	95	97
X15-3.1	94	93	96	97		94
X15-3.2	94	94	94	94	94	92
X15-3.3	94	94	99	93	94	99
Y16-3.1	97	97	96	97	95	97
Y16-3.2	97	98	22	96	97	97
Y16-3.3	97	95	100	98	99	100
Z17-3.1	95	97	100	99	98	99
Z17-3.2	96	98		98	98	97
Z17-3.3	97	97	96	97	98	97
A18.01	90	94	96	95	98	93
A18.02	86	89	88	97	92	94
A18.03	97	98	98	99	99	99
B19.01	90	100	99	98	99	97
B19.02	97	93	98	88	97	89
B19.03	97	95	97	95	97	96
D21.01	94	93	95	94	98	95
D21.02	97	92	93	88	92	91
D21.03	95	97	96	97	97	97
E22.01	84	93	93	90	83	95
E22.02	90	87	92	98	85	
E22.03	93	96	93	96	96	95
J24.01	89	91	93	93	90	91
J24.02	84	83	90	90	95	96
J24.03	93	97	92	95	96	94
K25.01	92	96	97	97	96	94

Oxidative Burst (%)	Baseline	IP	R15	R30	R45	R60
K25.02	93	96	96	98	95	98
K25.03	95	94	95	98	94	98
M26.01	91	96	95	98	96	96
M26.02	97	97	96	98	98	98
M26.03	99	98	98	98	99	99
P27.01	93	95	95	95	96	93
P27.02	98	99	100	98	100	99
P27.03	98	100	98	99	98	100
R28.01	87	84	91	90	83	91
R28.02	92	83	88	86	90	91
R28.03	92	94	93	94	93	92
Z29.01	93	93	95	94	98	93
Z29.02	99	98	97	99		
Z29.03	100	100	100	99	99	99
A30.01	99	99	100	99	99	100
A30.02	89	92	95	95	90	98
A30.03	93	97	94	100	94	91
B31.01	98	98	99	99	99	99
B31.02	86	93	91	91	88	96
B31.03	96	92	93	93	91	99
C32.01	98	98	99	99	100	99
C32.02	82	87	83	83	84	83
C32.03	95	94	93	93	96	95
D33.01	100	99	99	99	98	
D33.02	86	94	95	92	94	91
D33.03	93	83	97	92	94	90
H34.01	98	98	99	99	99	99
H34.02	85	92	93	90	93	94
H34.03	92	100	97	94	94	97
J35.01	100	99	100	99	99	99
J35.02	93	93	96	99	98	96
J35.03	91	92	96	96	97	95
K36.01	99	99	97	98	100	99
K36.02	86	85	89	89	82	86
K36.03	86	87	89	91	94	89
M37.01	97	100	99		99	99
M37.02	72	82	80	82	83	85
M37.03	92		94	86	93	98
O38.01	98	100	99	100	99	100
O38.02	96	96	97	94	96	98
O38.03	99	95	99	97	98	99

Visit 1

	Heart Rate			Time (min) in Heart Rate Zones				
Subject	Peak	Base	Average	<60% MHR	60-70% MHR	70-80% MHR	80-90% MHR	>90% MHR
B01-1	176	74	122	21.6	13.9	12.9	6.3	0.0
E02-1	178	90	136	15.3	9.0	14.2	15.7	0.5
Z03-1	181	67	130	19.7	9.4	14.9	10.3	0.6
G04-1	191	68	133	21.5	6.9	11.2	10.0	5.8
P05-1	195	90	145	12.4	7.8	10.6	15.1	8.4
P06-1	217	39	125	22.9	4.0	6.5	9.3	12.5
G07-1	166	77	116	30.4	17.9	6.1	0.9	0.0
R08-2	202	91	156	1.1	6.8	17.8	19.6	9.3
R09-2	204	116	163	0.3	2.0	17.1	19.7	16.4
W10-2	182	85	133	10.2	23.5	12.0	7.7	0.7
S11-3	222	79	132	18.8	19.1	8.6	11.8	3.5
T12-3	200	84	154	1.5	13.3	19.0	12.2	15.5
C13-3	210	93	135	15.5	22.7	9.1	10.3	4.4
W14-3	218	95	151	1.2	13.7	21.1	17.8	7.6
X15-3	217	82	152	2.9	13.5	17.9	14.2	13.6
Y16-3	193	82	131	24.1	11.5	11.3	11.6	3.4
Z17-3	196	81	143	7.0	22.2	10.3	11.1	10.6
A18-04	200	45	141	9.3	7.5	7.8	8.0	11.5
B19-04	201	68	157	1.3	4.4	14.1	14.3	10.1
D21-04	192	73	142	6.8	10.9	11.2	12.6	2.8
E22-04								
J24-05	193	75	142	12.2	20.7	4.9	14.2	9.3
K25-05	191	41	132	22.8	16.1	3.2	9.3	9.4
M26-05	240	73	146	11.2	20.9	6.3	12.3	11.2
P27-05	218	80	146	1.8	25.4	12.2	12.2	9.4
R28-05	199	74	136	22.7	12.9	4.3	10.8	11.2
Z29-05	194	79	141	14.6	20.8	4.1	7.3	15.8
A30-06	236	85	146	13.2	15.9	6.4	5.7	18.6
B31-06	239	85	140	8.6	25.7	6.8	11.9	5.8
C32-06	201	96	146	10.0	19.9	7.7	3.2	19.1
D33-06	187	79	135	15.3	21.1	6.9	8.8	7.2
H34-06	193	96	143	1.3	31.1	6.3	14.8	6.5
J35-06	185	66	125	31.5	8.9	3.8	14.7	1.9
K36-06	192	77	141	12.0	16.7	12.1	2.7	15.7
M37-06	191	79	147	4.5	20.1	13.5	5.1	16.0
038-06	186	68	129	30.1	6.9	2.8	16.0	3.4

Visit 2

	Heart Rate			Time (min) in Heart Rate Zones				
Subject	Peak	Base	Average	<60% MHR	60-70% MHR	70-80% MHR	80-90% MHR	>90% MHR
B01-1	180	66	102	34.9	2.2	0.3	3.5	2.3
E02-1	179	76	100	35.2	2.5	0.5	4.6	1.0
Z03-1	196	87	139	8.3	8.8	11.7	8.8	4.7
G04-1	187	78	122	14.7	7.3	5.2	4.9	1.3
P05-1	196	84	131	17.0	6.4	6.0	7.9	5.7
P06-1	204	99	147	7.4	5.1	5.4	7.3	8.7
G07-1	167	86	111	21.2	6.4	4.9	1.6	0.0
R08-2	190	102	138	20.5	4.8	5.2	15.0	6.8
R09-2	198	104	128	25.5	7.1	4.5	8.9	6.1
W10-2	169	79	105	38.2	6.2	6.0	3.5	0.0
S11-3	227	81	130	31.2	4.7	1.9	21.9	3.4
T12-3	203	86	145	8.6	24.8	2.8	3.7	20.5
C13-3	202	85	136	23.4	11.3	3.2	17.0	6.7
W14-3	200	100	148	1.6	24.7	13.5	5.0	16.2
X15-3	196	111	151	7.5	18.3	8.1	4.8	22.5
Y16-3	226	27	131	31.1	4.4	1.5	15.5	9.7
Z17-3	205	72	148	6.8	21.7	6.9	4.2	21.4
A18-04	190	93	138	8.5	15.4	8.2	7.0	4.5
B19-04	215	100	150	5.5	8.7	8.3	11.2	9.3
D21-04	195	73	131	18.5	8.6	4.9	4.9	7.0
E22-04	161	44	99	27.6	7.7	7.0	2.5	0.0
J24-05	191	105	164	1.0	1.5	12.6	23.9	14.7
K25-05	189	78	154	5.0	9.0	9.9	12.8	18.2
M26-05	222	77	156	4.1	5.7	14.6	17.3	12.4
P27-05	225	97	160	2.5	4.5	11.5	21.6	14.0
R28-05	190	71	157	2.0	6.0	12.9	21.8	11.2
Z29-05	191	96	160	1.8	5.7	9.4	22.1	14.1
A30-06	199	82	135	8.5	21.1	17.1	5.7	2.7
B31-06	192	90	142	2.5	18.6	23.0	8.6	2.4
C32-06	232	100	141	12.9	14.4	10.3	11.0	7.7
D33-06	181	75	115	36.2	13.2	4.0	1.9	0.4
H34-06	190	92	143	2.6	10.6	33.4	7.6	1.7
J35-06	176	70	119	26.4	19.3	7.8	2.6	0.1
K36-06	191	36	118	20.0	19.3	12.9	1.9	1.9
M37-06	191	77	144	5.5	18.7	13.1	4.2	14.3
038-06	186	74	115	33.3	16.4	3.9	1.3	1.1

Visit 3

	Heart Rate			Time (min) in Heart Rate Zones				
Subject	Peak	Base	Average	<60% MHR	60-70% MHR	70-80% MHR	80-90% MHR	>90% MHR
B01-1	173	70	146	0.9	5.4	10.1	7.7	0.0
E02-1	171	73	127	9.4	5.8	4.6	5.1	0.0
Z03-1	191	76	148	1.0	7.2	7.1	5.5	3.9
G04-1	195	99	139	10.7	7.9	10.9	9.0	5.0
P05-1	204	87	168	0.3	0.0	4.8	10.5	8.7
P06-1	204	93	144	10.2	11.0	3.6	6.9	11.2
G07-1	176	89	110	35.0	2.0	1.0	6.4	0.0
R08-2	211	84	124	20.0	7.3	5.0	6.1	3.8
R09-2	217	109	149	10.2	10.3	5.1	5.0	17.5
W10-2	196	85	118	25.2	11.6	5.4	3.9	2.6
S11-3	239	69	130	31.2	5.6	3.3	12.6	5.6
T12-3	193	38	140	5.0	23.1	13.2	4.0	12.6
C13-3	240	45	136	32.2	8.4	0.6	0.3	18.2
W14-3	212	64	133	10.7	17.6	13.4	10.9	5.4
X15-3	233	82	155	0.8	23.3	10.3	1.4	22.9
Y16-3	197	53	131	27.8	9.4	3.4	13.0	5.3
Z17-3	196	74	141	13.7	17.8	5.9	8.0	12.0
A18-04	198	138	175	0.0	0.2	5.2	17.0	34.6
B19-04	192	96	166	0.0	1.2	13.5	27.1	15.1
D21-04	205	88	163	0.9	5.3	14.1	16.3	19.5
E22-04	192	56	148	5.3	8.9	19.0	15.4	7.3
J24-05	192	77	140	5.6	8.0	16.2	5.5	3.4
K25-05	180	48	125	11.5	14.1	7.8	4.1	0.7
M26-05	180	72	142	5.8	4.0	13.5	14.8	0.5
P27-05	217	80	143	6.3	5.5	15.1	8.0	3.3
R28-05	195	78	142	4.0	9.1	14.8	5.8	4.3
Z29-05	197	100	162	1.4	2.0	5.4	21.2	8.3
A30-06	194	51	127	23.8	5.9	4.6	8.0	6.7
B31-06	179	100	140	5.8	14.2	13.1	14.4	0.4
C32-06	193	74	138	15.0	9.6	6.6	8.6	8.8
D33-06	168	78	99	36.6	7.5	5.0	1.2	0.0
H34-06	187	41	136	6.4	14.2	15.0	10.7	2.8
J35-06	215	67	123	24.9	7.8	8.6	6.0	2.2
K36-06	178	27	110	28.5	8.7	7.9	4.3	0.4
M37-06	224	76	154	1.0	16.2	7.6	11.0	13.5
038-06	176	42	111	30.3	7.9	6.5	5.2	0.1