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UNIVERSITY OF MIAMI

DIFFERENCES IN RESTING AND EXERCISING PULMONARY FUNCTION AMONG SEDENTARY, RESISTANCE-TRAINED AND AEROBICALLY-TRAINED, EARLY SYMPTOMATIC, HIV-1 SEROPOSITIVE MEN

By

Craig C. Talluto

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

May 2009

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Craig C. Talluto

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(May 2009)

Differences in Resting and Exercising Pulmonary Function among Sedentary, Resistance-Trained and Aerobically-Trained, Early Symptomatic, HIV-1 Seropositive Men

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor Arlette Perry.
No. of pages in text (104).

The human immunodeficiency virus (HIV)-1 can compromise pulmonary function at all stages of the disease. The present study examined whether there were differences in resting and exercising pulmonary function among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1^+ men. Forty five subjects, 15 per group, were enrolled. An analysis of variance (ANOVA) showed differences in demographics for age [$F(2, 42) = 5.14$, $p<0.01$)], weight [$F(2, 42) = 4.84$, $p<0.01$)], body mass index [$F(2, 42) = 9.50$, $p<0.01$)] and average years HIV-1^+ [$F(2, 42) = 4.78$, $p<0.01$)]. A multiple analysis of covariance (MANCOVA) showed differences in resting pulmonary function [$F(8, 72) = 7.164$, $P = 0.01$]. Univariate ANOVA's and Bonferroni post-hoc comparisons showed the aerobically-trained group had higher forced expiratory volume in one second (FEV_1) than the resistance-trained and sedentary groups ($p<0.05$ and $p<0.01$, respectively), higher forced vital capacity (FVC) ($p<0.01$, for both), higher maximum voluntary ventilation ($p<0.01$, for both) and higher FEV_1/FVC ratios than the sedentary group only ($p<0.01$). The resistance-trained group also showed higher FEV_1 ($p<0.01$) and FEV_1/FVC ($p<0.01$) than the sedentary group.

For exercising pulmonary function, significant differences in our MANCOVA were found [F (12, 68) = 12.73, P = 0.001]. Univariate ANOVA's and Bonferroni post-hoc comparisons showed that the aerobically-trained group had higher dyspnea index than the resistance-trained and sedentary groups ($p<0.01$ and $p<0.05$, respectively), higher ventilatory efficiency ($RR/\dot{V}E_{max}$) than the resistance-trained and sedentary groups ($p<0.05$ and $p<0.01$, respectively), higher maximum minute ventilation ($\dot{V}E_{max}$) ($p<0.01$, for both), higher peak oxygen consumption (peak $\dot{V}O_2$) ($p<0.01$, for both) and lower dead space (V_D/V_T) ($p<0.01$, for both). The resistance-trained group also showed higher peak $\dot{V}O_2$ ($p<0.01$), lower V_D/V_T ($p<0.01$) and lower $RR/\dot{V}E_{max}$ ($p<0.01$) than the sedentary group. Results suggest that aerobically-trained, and to a lesser extent, resistance-trained seropositives possessed superior resting and exercising pulmonary function compared to sedentary seropositive males.

DEDICATION

Thank you to Mary E. Talluto for your unwavering support of me throughout my life. You have been such an inspiration to me and have always encouraged me to follow my heart.

Thank you to José Carlos Torres for your unwavering support of me throughout this challenging time. I am so grateful that you are part of my life.

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Thank you to Dr. Arlette Perry for guiding me through this process and giving me the encouragement needed to complete this study.

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Thank you to Drs. Joseph Signorile and Kent Burnett for being on my dissertation committee and providing appropriate feedback so I could complete this study.

Thank you to all the subjects who volunteered for this study and who willingly underwent effort-dependent resting and exercising pulmonary function tests in an effort to help understand the relationship between pulmonary function and HIV-1 disease. Hopefully, we have learned more about this relationship and can use this to help improve the quality of life of all those infected with HIV-1 disease.

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CHAPTER ONE: INTRODUCTION

Overview

It is well recognized that the human immunodeficiency virus (HIV)-1 compromises pulmonary function even in the early stages of HIV-1 disease, before the advent of overt pulmonary disease (Pothoff, Wasserman & Ostmann, 1994; Mitchell, Flemming, Pinching, Harris, Moss, Veale & Shaw, 1992). Individuals who are HIV-1 seropositive are subject to frequent pulmonary infections due to a myriad of opportunistic and common pathogens (O'Donnell, Bader, Zibrak, Jesen & Rose, 1988). Pulmonary complications occur in over 40% of persons infected with HIV-1 disease (Camus, de Picciotto, Gerbe, Matheron, Perronne & Bouvet, 1993; Shaw, Roussak, Forster, Harris, Pinching & Mitchell, 1988) and pulmonary disorders often complicate infection in HIV-1 seropositive patients (Rosen, Lou, Kvale, Rao, Jordan, Miller, Glassroth, Reichman, Wallace & Hopewell, 1995).

A physician's first encounter with most HIV-1 seropositive patients is usually an acute infection of the lungs, central nervous system or gastrointestinal tract (Donath & Khan, 1987). The lungs constitute principal targets of the infectious and noninfectious complications of HIV infection. The depletion of $CD4^+$ T-cells and the subsequent abrogation of the immune system by HIV-1 greatly facilitate the development of opportunistic microorganisms in the lung. The spectrum of pulmonary diseases associated with HIV continues to broaden, with more than 80% of acquired immunodeficiency (AIDS) patients having pulmonary disorders of some nature, 90% of which are infectious. In fact, almost 70% of individuals infected with HIV-1 disease will have at least one respiratory episode during the course of their disease and at necropsy. The lungs

are affected by AIDS-related processes in approximately 90% of the patients (Miller, 1996).

The potential problems in pulmonary function demonstrate an overwhelming need to evaluate the possible decrease in functional pulmonary capacity to determine if values are compromised. Therefore, the use of pulmonary function tests (PFT) may be critical if limitations of the respiratory system are severe enough to restrict the activities of daily living. A study conducted by O'Donnell, et al., 1988, using a homogeneous sample of AIDS-defined subjects, determined that 44 out of 105 (42%) of the AIDS-defined patients had abnormal airway function. A mechanical obstruction was present in association with a forced vital capacity (FVC) of less than 80% of predicted in 14% of these patients. An additional 57% of these patients had abnormally low ratios of forced expiratory volume in one second (FEV_1) over FVC. Furthermore, a study at the University of Miami's Center for Exercise Medicine reported that there were statistically significant differences in resting pulmonary variables (FVC, FEV_1, maximum voluntary ventilation (MVV), peak expiratory flow (PEF) and vital capacity (VC)) between early symptomatic, HIV-1 seropositive men and seronegative controls (Talluto, LaPerriere, Perry, Klimas, Goldstein, Majors, Ironson, Fletcher & Schniederman, 1999).

Although resting PFTs do detect and quantify functional abnormalities of the lung (Basson & Stewart, 1991), limitations to work may not be completely predicted from single or multiple measures of pulmonary function performed at rest. Exercise testing provides a more important determinant of lung function during the performance of work-related tasks (Wiedemann, 1991) since it evaluates lung function and cardiac work during increasing metabolic demands (Jones, 1988). Therefore, tests designed to assess

ventilation, gas exchange and cardiovascular function during exercise can provide additional information to that obtained at rest and may be quite valuable to the working population (Wanger, 1996).

Graded exercise testing (GXT) provides a standardized, reliable method for assessing pulmonary function in response to exercise. GXT's have been found to be a useful technique when evaluating the degree, and in many instances, the etiology of exercise intolerance (Johnson, Anders, Blanton, Hawkes, Bush, McAllister &g Matthews, 1990). The determination of maximum oxygen consumption ($\dot{V}O_{2\ max}$) may be considered the most important "lung function test" for assessing pulmonary impairment (Wiedemann, 1991), and may also provide ancillary information when traditional resting lung function measurements do not adequately explain symptoms during work (Wiedemann, 1991). While mild lung disease may not reduce $\dot{V}O_2$, it may reduce the "ventilatory reserve" that exists at peak exercise.

In healthy populations, exercise is commonly used to increase cardiovascular capacity and minimize the effects of cardiovascular and pulmonary disease. Pollock & colleagues (1998) reported that healthy individuals who participated in regular aerobic exercise had higher exercising lung function values than sedentary controls. Since exercise training has a positive affect on respiratory function, it has been used as a behavioral intervention strategy in an attempt to delay pulmonary problems associated with HIV-1 disease. Several studies, using aerobic exercise and/or resistance training as an intervention strategy, have observed increases in aerobic capacity, strength and/or relevant immunological markers of seropositive subjects (LaPerriere, Antoni, Klimas, Ironson & Schneidermann, 1991; Birk & MacArthur, 1994; MacArthur, Levine & Birk, 1993;

Spence, Galantino, Mossberg & Zimmerman 1990; Lox, McAuley & Tucker 1995; Stringer, Berezonskaya, O'Brien, Bech & Casaburi, 1998; Stringer, 2000; Klemack, 2007), however, none of the aforementioned studies examined the effects of aerobic exercise and/or resistance-training on lung function in HIV-1 disease. This is unfortunate since 70% of the seropositive population experiences their first opportunistic infection as a result of HIV-1 disease in the lung. Therefore, it would be relevant to determine if previously trained in comparison to untrained HIV-1 seropositive subjects have enhanced lung function values both at rest and during exercise. It would also be germane to determine if resistance or aerobic training plays an important role in resting or exercising pulmonary function in those affected with the HIV-1 disease. The purpose of this study was to determine if there were any significant differences in resting and exercising pulmonary function between sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men.

Statement of the Problem

Due to the frequent and often fatal pulmonary complications experienced by HIV-1 seropositive individuals (O'Donnell, et al., 1988), it is critical to diagnose potential pulmonary infections as early as possible. Past research has shown improvements in aerobic capacity, strength and immunological markers of HIV-1 seropositive patients when they have participated in exercise training. However, the most appropriate type of exercise training has not been clarified with respect to pulmonary function. The purpose of this study was to determine if there were any significant differences in resting and

exercising pulmonary function among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men.

(1) Null Hypothesis: There are no significant differences in resting pulmonary function values among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men. These include FVC, FEV_1, FEV_1/FVC and MVV.

(2) Null Hypothesis: There are no significant differences in maximum exercising pulmonary function values among sedentary, resistance-trained and aerobically trained, early symptomatic, HIV-1 seropositive men. These include maximum minute ventilation ($\dot{V}E_{max}$), peak O_2 uptake (peak $\dot{V}O_2$), shortness of breath known as the dyspnea index (DI) ($\dot{V}E_{max}$/MVV x 100), dead space to tidal volume ratio (V_D/V_T), ventilatory equivalent for carbon dioxide (CO_2) ($\dot{V}E_{max}/\dot{V}CO_2$) and respiratory rate (RR) as a function of $\dot{V}E_{max}$ ($RR/\dot{V}E_{max}$).

Delimitations

This study is delimited to:

(1) HIV-1 seropositive men from diverse ethnic and racial backgrounds, i.e., Caucasian, Hispanic, and African-American men.

(2) HIV-1 seropositive men between the ages of 18 and 45.

(3) Early symptomatic diagnosis confirmed by a $CD4^+$ cell count of $\geq$ 200 cells/μL but < 500 cells/μL.

(4) No prior history of bronchitis, emphysema, asthma, or smoking.

(5) Resting FVC, FEV_1, FEV_1/FVC and MVV collected using a SensorMedics 2130 computerized spirometer.

(6) The average of the two best of the 3 trials used to assess FVC, FEV_1 and FEV_1/FVC.

(7) The best of the two trials used to assess MVV.

(8) $\dot{V}E_{max}$, peak $\dot{V}O_2$, DI, V_D/V_T, $\dot{V}E_{max}/\dot{V}CO_2$ and $RR/\dot{V}E_{max}$ measures made during a GXT on an Ergoline 800 electronically-braked stationary bicycle ergometer.

(9) Physically capable of performing a GXT to maximum.

(10) Aerobically-trained, HIV-1 seropositive men who have been participating in aerobic exercise only 3 or more times a week, for a minimum of six months and have achieved good or high peak $\dot{V}O_2$ values during the GXT (American College of Sports Medicine (ACSM), 2000).

(11) Resistance-trained, HIV-1 seropositive men who have been training with weights only 3 or more times a week, for a minimum of six months and have achieved average, fair or low peak $\dot{V}O_2$ values during the GXT (ACSM, 2000).

(12) Sedentary, HIV-1 seropositive men who have not exercised on a regular basis for six months or more and have achieved average, fair or low peak $\dot{V}O_2$ value during the GXT (ACSM, 2000).

Limitations

This study is limited by:

(1) the capacity of a SensorMedics 2130 computerized spirometer to adequately assess resting pulmonary function values.

(2) the use FVC, FEV_1, FEV_1/FVC and MVV to assess resting pulmonary function.

(3) the use of spirometric testing which may be affected by the subjects personal motivation and the ability of the technician to conduct the test so as to obtain maximal effort from the subject (Ruppel, 2003).

(4) the use of a hyperventilation technique to assess MVV as an index of peak exercise ventilatory capacity.

(5) the use of $\dot{V}E_{max}$, peak $\dot{V}O_2$, DI, V_D/V_T, $\dot{V}E_{max}/\dot{V}CO_2$ and $RR/\dot{V}E_{max}$ to assess peak pulmonary function during exercise.

(6) the use of a GXT to assess aerobic fitness which may be affected by the subjects personal motivation, local quadriceps pain and the ability of the technician to conduct the test so as to obtain maximal effort from the subject (ACSM, 2000).

(7) the use of an Ergoline 800 electronically-braked bicycle ergometer to determine cardiovascular fitness since this activity may be biomechanically dissimilar to movement patterns typical of subject's daily physical activity.

(8) the lack of incorporating strength training assessments (1-repetition maximum bench press and leg press tests) to confirm that the level of the resistance-trained group was above average [$\geq$ 60% of the normative values per ACSM, (2007)].

Significance of the Study

The World Health Organization (WHO) estimates the number of people living with HIV/AIDS worldwide to be approximately 33.2 million (WHO AIDS Epidemic Update, 2007). Furthermore, there are an estimated 1.03 million people living with HIV/AIDS in the United States since the beginning of the pandemic (CDC, 2007). In fact, the 2007 Surveillance Report from the Centers for Disease Control (CDC) reported 56,300 new cases of HIV-1 infection for the previous reporting year. With the vast number of persons currently living with HIV/AIDS, and the alarming number of newly reported HIV-1 cases, it is important to develop behavioral intervention strategies that may supplement the more traditional medical intervention procedures. Behavioral intervention strategies, in conjunction with traditional medicine, may delay the deleterious effects of HIV-1 disease.

Exercise is a behavioral intervention strategy that has received an abundance of recognition. In apparently healthy populations, individuals who have participated in an

exercise program have been shown to have improved exercising lung function when compared to sedentary controls (Pollock, Gaesser, Butcher, Despres, Dishman, Franklin & Ewing-Garber, 1998). In HIV-1 populations, aerobic exercise (LaPerriere, et al., 1991) and resistance training (Rigsby, Dishman, Jackson, MacLean & Raven, 1992; Lox, et al., 1995) have been shown to be successful in helping HIV/AIDS patients increase their strength, immunological markers, reduce stress and anxiety and delay or prevent lypodystrophy (HIV wasting syndrome). To date, however, there are no research projects examining the effects of aerobic exercise or resistance training on pulmonary function.

Clearly, it is important to determine if previous exercise training will provide some degree of protection from compromised lung function values in HIV-1 seropositive patients. This study identified the effects of resting and exercising pulmonary function values among previously trained (aerobic and resistance-trained) and sedentary HIV-1 seropositive men to determine if there were any significant differences in lung function among the three groups. It is possible that previous participation in a regular exercise program, in conjunction with traditional treatment regimens, may be associated with enhanced lung function in this population.

Definition of Terms

Medical and Immunologic Terms

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS): A life threatening disease caused by the human immunodeficiency virus (HIV) which renders the immune system ineffective. The manifestations of AIDS can be explained by the loss of helper T cell functions or the infection of other cells with CD4 molecules. Without T helper cells,

cytotoxic T and B-cell activation is impaired and specific resistance is suppressed. The most common clinical evidence of AIDS includes testing positive for HIV antibodies, a decrease in $CD4^+$ T-cell numbers of > 200 cells//μL and the presence of opportunistic infections, i.e., tuberculosis, recurrent pneumonia, kaposi sarcoma, etc (Kuby, 1994).

-HUMAN IMMUNODEFICIENCY VIRUS (HIV): A retrovirus responsible for the cause of AIDS. HIV is transmitted from an infected to non-infected person in body bodily fluids such as blood, semen, or vaginal secretions. The major modes of transmission are through unprotected, intimate sexual contact, contaminated needles used by intravenous drug users (IDU), and contaminated blood products (Abas, Lichtman & Pober, 1994).

ACUTE PRIMARY HIV INFECTION**:** Acute HIV infection is a condition that occurs 2 to 4 weeks after infection by the HIV virus. Acute HIV infection can resemble infectious mononucleosis, flu, or other viral syndromes. Typical symptoms include fever, headache, fatigue and swollen lymph nodes. Patients may also experience aching muscles and a rash that occurs anywhere on the body and may change locations. These symptoms may last from a few days up to 4 weeks, and then subside (Kuby, 1994).

ANTIBODY: Antibody molecules are plasma proteins that bind specifically to particular molecules known as antigens and are produced in response to immunization with antigens. They bind to and neutralize pathogens or prepare them for uptake and destruction by phagocytes. Each antibody molecule has a unique structure that allows it to bind its specific antigen, but all antibodies have the same overall structure and are known collectively as immunoglobulins (Kuby, 1994).

-IMMUNOGLOBULIN A (IgA): An antibody that plays a critical role in mucosal immunity. More IgA is produced than all other types of antibody combined. Because it is resistant to degradation by enzymes, IgA can survive in harsh environments such as the digestive and respiratory tracts, to provide protection against microbes that multiply in body secretions (Abas, et al., 1994).

-IMMUNOGLOBULIN G (IgG): A tetrameric immunoglobulin, built of two heavy chains γ and two light chains. Each IgG has two antigen binding sites. It is the most abundant immunoglobulin and is equally distributed in blood and tissue liquids, constituting 75% of serum immunoglobulins in humans. It can bind to many pathogens and protects the body against them by complement activation (classic pathway), opsonization for phagocytosis and neutralization of their toxins (Abas, et al., 1994).

ANTIGEN: An antigen is any substance that causes the immune system to produce antibodies against it. An antigen may be a foreign substance from the environment such as chemicals, bacteria, viruses, or pollen. An antigen may also be formed within the body, as with bacterial toxins or tissue cells (Kuby, 1994).

ASTHMA: A common disorder in which chronic inflammation of the bronchial tubes (bronchi) results in a narrowing of the airways. Asthma involves only the bronchial tubes and does not affect the air sacs (alveoli) or the lung tissue (the parenchyma of the lung) itself. Airway arrowing in asthma is due to three major processes acting on the bronchi: inflammation, bronchospasm and hyperreactivity (Kuby, 1994).

ASYMPTOMATIC HIV-INFECTION: **A** phase of chronic HIV infection during which there are no symptoms of HIV infection. Asymptomatic HIV infection is a period of varying length in which the immune system slowly deteriorates without symptoms. The

length of this phase varies from person to person. It depends on how quickly the HIV virus is copying itself and the genetic differences that affect the way the immune system handles the virus. Some patients can go ten years or longer without symptoms, while others may have symptoms and worsening immune function within a few years after the original infection (Kuby, 1994).

BLOOD PRESSURE: The blood pressure is the pressure of the blood within the arteries. It is produced primarily by the contraction of the heart muscle. Its measurement is recorded by two numbers. The first number (systolic pressure) is a measure after the heart contracts and is the highest. The second number (diastolic pressure) is a measure before the heart contracts and is the lowest. (Kuby, 1994).

BRONCHITIS: An inflammation of the lining of the bronchial tubes (the airways that connect the trachea (windpipe) to the lungs). This delicate, mucus-producing lining covers and protects the respiratory system, the organs and tissues involved in breathing. When a person has bronchitis, it may be harder for air to pass in and out of the lungs than it normally would, the tissues become irritated and more mucus is produced (Abas, et al., 1994). Acute bronchitis is a condition caused by viruses or bacteria and can last several days or weeks. Chronic bronchitis is a persistent, productive cough lasting at least three months in two consecutive years (Kuby, 1994)

CLUSTERS OF DIFFERENTIATION (CD): Antibodies that satisfy the specified criteria for the definition of a new antigen are officially recognized and the identified antigen is assigned the CD symbol which stands for “cluster of differentiation” (a group of antigens that differentiate leukocyte populations) (Kuby, 1994). They are groups of monoclonal antibodies that identify the same cell-surface molecule.

-CD4**:** The $CD4^+$ molecule is expressed on T lymphocytes that recognize antigen in the context of class II MHC (major histocompatibility complex) molecules. Many of these lymphocytes are helper and inducer cells (Kuby, 1994). $CD4^+$ T-cells can help B-cells make an antibody in response to antigenic challenge. The most efficient helper T-cells are known as T_H2 cells that make cytokine intereleukins (IL)-4 and IL-5 (Abas, et al., 1994).

ELECTROCARDIOGRAM: A recording of the electrical activity of the heart. An electrocardiogram is a simple, non-invasive procedure. Electrodes are placed on the skin of the chest and connected in a specific order to a machine that, when turned on, measures the electrical activity of the heart (West, 1997).

EMPHYSEMA: Emphysema is a type of chronic obstructive pulmonary disease (COPD) involving damage to the air sacs (alveoli) in the lungs. As a result, the body does not get the oxygen it needs. Patients with emphysema report increases in dyspnea, may experience a chronic cough and have trouble breathing during exercise (Abas, et al., 1994)

HYPERTENSION: Defined as a repeatedly elevated blood pressure exceeding 140 over 90 mmHg (a systolic pressure above 140 with a diastolic pressure above 90) (West, 1997).

IMMUNE SYSTEM: The immune system is a collection of mechanisms within an organism that protects against disease by identifying and killing pathogens and tumor cells. It detects a wide variety of agents, from viruses to parasitic worms, and needs to

distinguish them from the organism's own healthy cells and tissues in order to function properly (Abas, et al., 1994).

INFLUENZA: An acute viral infection involving the respiratory tract, occurring in isolated cases, in epidemics, or in pandemics striking many continents simultaneously or in sequence. It is marked by inflammation of the nasal mucosa, the pharynx and conjunctiva, and by headache and severe, often generalized myalgia. Fever, chills and prostration are common. A necrotizing bronchitis and interstitial pneumonia are prominent features of severe influenza and account for the susceptibility of patients to secondary bacterial pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus* (commonly seen in advanced HIV disease). The incubation period is one to three days and the disease ordinarily lasts for three to ten days. Influenza is caused by a number of serologically distinct strains of virus, designated A (with many subgroups), B, and C (Kuby, 1994).

INTERSTITIAL LUNG DISEASE: A syndrome of fever, cough, and dyspnea, with bibasilar pulmonary infiltrates consisting of dense interstitial accumulations of lymphocytes and plasma cells. It is often associated with HIV, autoimmune and lymphoproliferative disorders (Kuby, 1994).

LYMPH NODES: Lymph nodes are small, bean-shaped, soft nodules that are not usually visible or easily felt. They are located in clusters in various parts of the body, such as the neck, armpit and groin. Lymph nodes produce lymphocytes, monocytes and plasma cells. They also filter the lymph fluid and remove foreign material, such as bacteria and cancer cells. When bacteria are recognized in the lymph fluid, the lymph nodes enlarge

as they produce and supply additional white blood cells to help fight infection (Abas, et al., 1994).

LYPODYSTROPHY: Lypodystrophy is a medical condition characterized by abnormal or degenerative conditions of the body's adipose tissue (Kuby, 1994).

MACROPHAGES: A type of white blood that ingests foreign material. Macrophages are key players in the immune response to foreign invaders such as infectious microorganisms. Blood monocytes migrate into the tissues of the body and there differentiate (evolve) into macrophages. Macrophages help destroy bacteria, protozoa and tumor cells. They also release substances that stimulate other cells of the immune system and are involved in antigen presentation. To do this, they carry the antigen on their surface and present it to a T cell (Abas, et al., 1994).

PNEUMOCYSTIS CARINII PNEUMONIA (PCP): A form of pneumonia caused by the yeast-like fungus and is relatively rare in people with normal immune systems but common among people with weakened immune systems. Symptoms include fever, non-productive cough, shortness of breath (especially on exertion), weight loss and night sweats (Kuby, 1994).

PULMONARY EDEMA: Pulmonary edema is a condition in which fluid accumulates in the lungs, usually because the hearts left ventricle does not pump adequately. The build-up of fluid in the spaces outside the blood vessels of the lungs is called pulmonary edema. Pulmonary edema is a common complication of heart disorders, and most cases of the condition are associated with heart failure. Pulmonary edema can be a chronic condition, or it can develop suddenly and quickly become life threatening (Kuby, 1994).

PULMONARY FIBROSIS: Scarring throughout the lungs which can be caused by many conditions such as sarcoidosis, hypersensitivity pneumosistis, asbestosis and certain medications. Symptoms of pulmonary fibrosis include shortness of breath, coughing and diminished exercise tolerance (Kuby, 1994);

PATHOGEN: An organism that causes disease (Abas, et al., 1994).

RETROVIRUS: A retrovirus is a virus that does not travel and enter host cells with a DNA genome, but an RNA genome. The most common way the RNA genome is replicated is via the enzyme reverse transcriptase to make DNA out of its RNA genome. The DNA is then incorporated into the host's genome by an integrase enzyme. The virus thereafter replicates as part of the host cell's DNA. Retroviruses are enveloped viruses that belong to the viral family *Retroviridae*.

SEROPOSITIVE: **A c**ondition in which antibodies to a specific antigen are found in the blood. In HIV/AIDS, the patient is considered seropositive when he/she tests positive for the HIV antibody, indicating exposure to the virus (Kuby, 1994).

SINUSITIS: A disorder of the sinuses, where one or more of the sinuses are inflamed. Acute sinusitis typically lasts 3 to 8 weeks, whereas chronic sinusitis, as typically seen in HIV-1 patients, lasts longer (Kuby, 1994)

VIRUS: Particles with a nucleic acid genome that must replicate in a living cell. Viruses are not able to carry out metabolic processes on their own (Abas, et al., 1994)

Respiratory System Terms

AIRWAY CONDUCTANCE: The instantaneous rate of gas flow in the airway per unit of pressure difference between the mouth, nose or other airway opening and the alveoli. It is the reciprocal of airway resistance (van der Graff & Fox , 1992).

AIRWAY HYPERRESPONSIVENESS: The term used to describe airways that narrow too easily and too much in response to challenge with nonspecific contractile agonists. Typically, a graph of airways resistance vs. dose is sigmoid in shape; the response shows a plateau at high levels of contractile stimulus. Generally, the existence of the plateau is interpreted to mean that the airway smooth muscle is activated maximally and, therefore, has shortened as much as it can against a given elastic load. Once on the plateau, any further increase in stimulus can not produce additional active force, muscle shortening or airway resistance (Abas, et al., 1994).

ALVEOLAR DEAD SPACE: The difference between physiological dead space and anatomical dead space, representing that part of the physiological dead space resulting from ventilation of relatively underperfused or nonperfused alveoli (van der Graff & Fox, 1992).

ALVEOLAR DUCTS: Alveolar ducts are the tiny end ducts of the branching airways that fill the lungs. There is approximately 1.5 to 2 million alveolar ducts in each lung. The tubules divide into two or three alveolar sacs at the distal end. They are formed from the confluence openings of several alveoli. Distal terminations of alveolar ducts are atria which then end in alveolar sacs (van der Graff & Fox, 1992).

ALVEOLAR VENTILATION: The amount of air that reaches the alveoli and is available for gas exchange with the blood per unit time (van der Graff & Fox, 1992).

ALVEOLI: The alveoli are the final branches of the respiratory tree and act as the primary gas exchange units of the lung. The gas-blood barrier between the alveolar space and the pulmonary capillaries is extremely thin, allowing for rapid gas exchange. To reach the blood, oxygen must diffuse through the alveolar epithelium, a thin interstitial space, and the capillary endothelium. Carbon dioxide follows the reverse course to reach the alveoli. There are two types of alveolar epithelial cells. Type I cells have long cytoplasmic extensions which spread out thinly along the alveolar walls and comprise the thin alveolar epithelium. Type II cells are more compact and are responsible for producing surfactant, a phospholipid which lines the alveoli and serves to differentially reduce surface tension at different volumes, contributing to alveolar stability (van der Graff & Fox, 1992).

BODY PLETHYSMOGRAPHY: A very sensitive lung measurement used to detect lung pathology that might be missed with conventional pulmonary function tests. This method of obtaining the absolute volume of air within one's lungs may also be used in situations where several repeated trials are required or where the patient is unable to perform the multi-breath tests (West, 1997).

BRONCHI: Bronchus (plural bronchi, adjective bronchial) is a caliber of airway in the respiratory tract that conducts air into the lungs. No gas exchange takes place in this part of the lung. (van der Graff & Fox, 1992).

BRONCHIOLES: The bronchioles or bronchioli are the first airway branches that no longer contain cartilage. They are branches of the bronchi, and are smaller than one millimeter in diameter. There are no glands or cartilage in any of the bronchioles, and the epithelial cells become more cuboidal in shape. The bronchioles terminate by entering

the circular sacs called alveoli. Control of airflow resistance and air distribution in the lungs is controlled by the bronchioles (van der Graff & Fox, 1992).

CAPILLARIES: Capillaries are the smallest of the body's blood vessels, measuring 5-10 μm in diameter, which connect arterioles and venules, and enable the interchange of water, oxygen, carbon dioxide and many other nutrient and waste chemical substances between blood and surrounding tissues (van der Graff & Fox, 1992).

CARTILAGE: A type of dense connective tissue. It is composed of specialized cells called chondrocytes that produce a large amount of extracellular matrix composed of collagen fibers, abundant ground substance rich in proteoglycan and elastin fibers. Cartilage is classified in three types, elastic cartilage, hyaline cartilage and fibrocartilage, which differ in the relative amounts of these three main components. Cartilage is found in many areas in the body including the articular surface of the bones, the rib cage, the ear, the nose, the bronchial tubes and the intervertebral discs. Its mechanical properties are intermediate between bone and dense connective tissue like tendon. Unlike other connective tissues, cartilage does not contain blood vessels. The chondrocytes are fed by diffusion, helped by the pumping action generated by compression of the articular cartilage or flexion of the elastic cartilage (van der Graff & Fox, 1992).

.CHEST X-RAY: A projection radiograph of the chest used to diagnose pulmonary problems within that area (West, 1997).

CHRONIC OBSTRUCTIVE LUNG DISEASE (COPD): A progressive disease that makes it hard to breathe. "Progressive" means the disease gets worse over time. COPD can cause coughing that produces large amounts of mucus, wheezing, shortness of breath, chest tightness, and other symptoms. In COPD, less air flows in and out of the airways

because the airways and air sacs lose their elastic quality, the walls between many of the air sacs are destroyed, the walls of the airways become thick and inflamed (swollen) and/or the airways make more mucus than usual, which tends to clog the airways (West, 1997).

CILIA: The cilium (plural cilia) is an organelle found in eukaryotic cells. Cilia are tail-like projections extending approximately 5–10 micrometers from the cell body. There are two types of cilia: motile cilia, which constantly beat in a single direction, and non-motile or primary cilia, which typically serve as sensory organelles. Along with flagella, they make up a group of organelles known as undulipodia. Primary cilia may be viewed as sensory cellular antennae that coordinate a large number of cellular signaling pathways, sometimes coupling the signaling to ciliary motility or alternatively to cell division and differentiation.

DEAD SPACE: The volume of gas in the lungs that does not participate in gas exchange. It represents air in the lungs that is ventilated but not perfused by pulmonary capillary blood flow. The dead space can be divided into the conducting airways, or anatomic dead space and the nonperfused alveoli, or alveolar dead space. The combination of anatomic and alveolar dead space volumes constitute the respiratory, or physiological, dead space (Ruppel, 2003).

DEAD SPACE TO TIDAL VOLUME RATIO (V_D/V_T): The volume of ventilation remaining in the conducting airways and alveoli that is not perfused by functional pulmonary capillaries (van der Graff & Fox, 1992).

DIAPHRAGM: A sheet of muscle extending across the bottom of the ribcage. The diaphragm separates the thoracic cavity from the abdominal cavity. The diaphragm is

crucial for breathing and respiration. During inhalation, the diaphragm contracts, thus enlarging the thoracic cavity (the external intercostal muscles also participate in this enlargement) which reduces intra-thoracic pressure. When the diaphragm relaxes, air is exhaled by elastic recoil of the lung and the tissues lining the thoracic cavity (van der Graff & Fox, 1992).

DIFFUSION: A net transport of molecules from a region of higher concentration to one of lower concentration by random molecular motion. The result of diffusion is a gradual mixing of material. In a phase with uniform temperature, absent external net forces acting on the particles, the diffusion process will eventually result in complete mixing or a state of equilibrium (van der Graff & Fox, 1992).

DYSPNEA: A consciousness of difficulty in breathing (Ruppel, 2003).

DYSPNEA INDEX: An example of quantifying ventilation during exercise using routine pulmonary function measurements. It is calculated by dividing the $\dot{V}E_{max}$ by MVV and multiplying by 100. Values greater than 50% are consistent with severe dyspnea (Ruppel, 2003).

ELASTIC RECOIL: The difference between intrapleural pressure and alveolar pressure at a given lung volume under static conditions (van der Graff & Fox, 1992).

GAS EXCHANGE: Takes place at a respiratory surface (a boundary between the external environment and the interior of the body); for unicellular organisms, the respiratory surface is governed by Fick's law, which determines that respiratory surfaces must have a large surface area, a thin permeable surface and a moist exchange surface. Control of respiration is due to rhythmical breathing generated by the phrenic nerve in order to stimulate contraction and relaxation of the diaphragm during inspiration and

expiration. Ventilation is controlled by partial pressures of oxygen and carbon dioxide and the concentration of hydrogen ions. The control of respiration can vary in certain circumstances such as during exercise (van der Graff & Fox, 1992).

GASTROINTESTINAL (GI) TRACT: The digestive tract is the system of organs within multicellular animals that takes in food, digests it to extract energy and nutrients and expels the remaining waste. The major functions of the GI tract are ingestion, digestion, absorption, and defecation. In a normal human adult male, the GI tract is approximately 6.5 meters (20 feet) long and consists of the upper and lower GI tracts. The tract may also be divided into foregut, midgut and hindgut, reflecting the embryological origin of each segment of the tract (van der Graff & Fox, 1992).

HYPERVENTILATION: The state of breathing faster and/or deeper than necessary, bringing about lightheadedness and other undesirable symptoms often associated with panic attacks. Hyperventilation can also be a response to metabolic acidosis, a condition that causes acidic blood pH levels (West, 1997).

INSPIRATORY CAPACITY (IC): The inspiratory capacity is the largest volume of air that can be inspired from the end of a resting expiration (Ruppel, 2003). It is equivalent to the sum of V_T and the inspiratory reserve volume in one breath (West, 1997).

HYPERCAPNIA: An excess of carbon dioxide in the blood (Ruppel, 2003).

HYPOXEMIA: A deficient amount of oxygen in the blood (Ruppel, 2003).

LARYNX: An organ in the neck involved in protection of the trachea and sound production. The larynx houses the vocal folds, and is situated just below where the tract of the pharynx splits into the trachea and the esophagus (van der Graff & Fox, 1992).

LOWER RESPIRATORY TRACT: Consists of the lower part of the respiratory system including the larynx (voice box), trachea (wind pipe), bronchial tubes, bronchioles and lungs (van der Graff & Fox, 1992).

LUNG: The lung is the essential respiration organ in air-breathing animals. Their principal function is to transport oxygen from the atmosphere into the bloodstream, and to release carbon dioxide from the bloodstream into the atmosphere. This exchange of gases is accomplished in the mosaic of specialized cells that form millions of tiny, exceptionally thin-walled air sacs called alveoli (van der Graff & Fox, 1992).

LUNG COMPLIANCE: The ability of the lungs to stretch in a change in pulmonary volume relative to an applied change in pressure. It is also a measure of the distensibility of the lung. Lung compliance can be influenced by disease states. For instance, fibrosis in lungs makes the lungs stiffer, thereby, decreasing lung compliance. In emphysema, where many alveolar walls are lost resulting in the lungs becoming loose and floppy, only a small pressure difference is needed to maintain a large volume, thereby increasing lung compliance (van der Graff & Fox, 1992).

LUNG PARENCHYMA: The key elements of the lung which are essential to its functioning. The lung parenchyma is opposed to the connective tissue framework of the lung (West, 1997).

MAXIMUM OXYGEN CONSUMPTION ($\dot{V}O_{2\,max}$): Maximum oxygen consumption is defined as the maximum amount of oxygen consumed by the body during peak exercise. It is usually measured on a minute to minute basis during peak exercise and indicates one's maximal aerobic power. An individual's $\dot{V}O_{2\,max}$ is considered one of the best indicators of cardiovascular endurance. This stems from the fact that the aerobic

system supplies the majority of energy required of these types of exercise. The higher an individual's maximal aerobic power, the more successful he or she will perform in endurance events (Fox, Bowers & Fox, 1989).

MAXIMUM VOLUNTARY VENTILATION (MVV): The maximum amount of air expired in one minute. This is a test of the overall mechanical function of the respiratory system since it is influenced by the degree of movement of the respiratory muscles, the compliance of the lung-thorax system, the condition of the ventilatory control mechanisms, and the resistance offered by the airways and tissues (West, 1997).

MAXIMUM MINUTE VENTILATION ($\dot{V}E_{max}$): It is the total volume of gas expired per minute by the exercising subject, expressed in liters, body temperature pressure saturated (BTPS). At rest, the values average 5 to 10 L/min. During exercise, this value commonly exceeds 100 L/min in healthy individuals and may increase to more than 200 L/min in trained subjects. Ventilation increases linearly with increased workload. As higher levels of work are achieved, ventilation increases to facilitate the removal of CO_2 production (Ruppel, 2003). The tremendous increase in ventilation provides a mechanism for the removal of CO_2, the primary product of exercising muscles.

MEAN EXPIRATORY PRESSURE (MEP): The maximum expiratory pressure is the highest pressure developed during expiration against an occluded airway (West, 1997).

MEAN INSPIRATORY PRESSURE (MIP): The highest atmospheric pressure developed during inspiration against an occluded airway (West, 1997).

MECHANORECEPTORS: A sensory receptor that responds to mechanical pressure or distortion (van der Graff & Fox, 1992).

MUCOUS MEMBRANE: Linings, of mostly endodermal origin, involved in absorption and secretion (van der Graff & Fox, 1992).

OBSTRUCTIVE LUNG DISEASE (OLD): A category of respiratory diseases characterized by airway obstruction including asthma, bronchitis and chronic obstructive pulmonary disease (West, 1997).

PEAK EXPIRATORY FLOW (PEF): The maximum flow rate obtained during an FVC maneuver. It primarily measures large airway function. PEF is commonly used in clinical situations, in addition to FVC and FEV_1, to gauge maximal effort during spirometry (West, 1997).

PEAK FLOW: Upper limit of flow from the lungs, either inspiratory or expiratory (West, 1997).

PEAK OXYGEN CONSUMPTION (PEAK $\dot{V}O_2$): It is a measurement of how much oxygen your body takes in and uses (ml/kg/min). It is a key measure of your body's exercise potential (van der Graff & Fox, 1992).

PHARYNX: A fibromuscular tube which extends from the base of the skull to the lower border of the cricoid cartilage (at which point it becomes the esophagus). Portions of the pharynx lie posterior to the nasal cavity (nasal pharynx), oral cavity (oral pharynx) and larynx (laryngeal pharynx). The muscular walls of the pharynx are comprised of an outer layer made up of three circularly disposed muscles (van der Graff & Fox, 1992).

PULMONARY: Pertains to all of the functions of the lungs, i.e., ventilation, perfusion, immunity, etc (van der Graff & Fox, 1992).

PULMONARY FUNCTION TEST (PFT): A group of tests that measure how well the lungs take in and release air and how well they move oxygen into the blood (Ruppel, 2003).

RESPIRATORY: Pertains to respiration (the exchange of oxygen and carbon dioxide between the atmosphere and the cells of the body). This is only one of the many functions of the pulmonary (lungs) system (Ruppel, 2003).

RESPIRATORY EXCHANGE RATIO (RER): The ratio of expired $\dot{V}CO_2$ to $\dot{V}O_2$ at the mouth. It indicates ones ability to move gas into and out of the lungs and the degree of effort during exercise. RER normally varies between .70 and 1.00 and it decreases at the beginning of exercise and increases towards the end of exercise. During maximal effort, it may exceed one indicating that the major energy source is carbohydrates (West, 1997).

RESPIRATORY RATE: The frequency of breathing. During exercise, breathing may increase up to four-fold in most subjects. As breathing frequency increases, tidal volume and vital capacity increase. As the respiratory rate peaks during maximal exercise, V_T will level off and, in some cases, decrease (West, 1997).

RESPIRATORY RATE AS A FUNCTION OF MAXIMUM MINUTE VENTILATION ($RR/\dot{V}E_{max}$): A measure used during work to determine the efficiency of ventilation (Stringer, 2000).

RESTRICTIVE LUNG DISEASE (RLD): A category of diseases of the respiratory system. These include diseases of the lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract and of the nerves and muscles of breathing. Respiratory diseases range from mild and self-limiting such as the common cold to life-threatening such as bacterial pneumonia or pulmonary embolism. RLD is characterized by reduced lung volume,

either because of an alteration in lung parenchyma or because of a disease of the pleura, chest wall, or neuromuscular apparatus. In physiological terms, restrictive lung diseases are characterized by reduced total lung capacity (TLC), vital capacity or resting lung volume. Accompanying characteristics are preserved airflow and normal airway resistance, which are measured as the functional residual capacity (FRC). If RLD is caused by parenchymal lung disease, restrictive lung disorders are accompanied by reduced gas transfer, which may be marked clinically by desaturation after exercise (West, 1997).

RESIDUAL VOLUME (RV): The volume of air remaining in the lungs at the end of a maximal expiration (West, 1997).

SPIROMETER: Instrument used for measuring resting pulmonary function (Ruppel, 2003).

TOTAL LUNG CAPACITY (TLC): The maximum volume to which the lungs can be expanded with the greatest possible inspiratory effort; it is equal to the vital capacity (VC) plus the residual volume (RV) and is approximately 5800 ml (West, 1997).

TRACHEA: A bony tube that connects the nose and mouth to the lungs, and is an important part of the vertebrate respiratory system. When an individual breathes in, air flows into the lungs for respiration through the trachea. The trachea is comprised of 16 to 20 “c” shaped rings of cartilage and ligaments and is located at the front of the neck. The trachea begins at the lower part of the larynx and continues to the lungs, where it branches into the right and left bronchi (van der Graff & Fox, 1992).

TRACHEOBRONCHIAL TREE**:** An ananatomical structure in the chest, which appears like an upside-down tree, and is composed of the trachea and bronchi (van der Graff & Fox, 1992).

TIDAL VOLUME (V_T): The volume of air inspired or expired in one breath. A pulmonary function test measures V_T on the expired side of the breathing maneuver. V_T tends to increase during the GXT and eventually levels off or decreases as the GXT proceeds (Ruppel, 2003).

UPPER RESPIRATORY TRACT: The upper respiratory tract begins with the nose and oral cavity and ends at the branching of the trachea into two bronchi (van der Graff & Fox, 1992).

VENTILATORY CAPACITY: The maximal ability to move gas in and out of lungs and is usually quantified by measuring maximum expiratory flow rates. As such, the maximum expiratory flow is determined by elastic recoil of lung and resistance of intrathoracic airways and is greatest at high lung volumes where elastic recoil is greatest and airways resistance is minimal (West, 1997).

VENTILATORY EQUIVALENT FOR CARBON DIOXIDE: The ratio of the volume of air ventilating the lungs to the volume of carbon dioxide produced (Ruppel, 2003).

VENTILATORY REQUIREMENT: The amount of oxygen required by the body to complete a unit of work (Ruppel, 2003).

VENTILATORY RESERVE: Calculated by the difference in MVV and $\dot{V}E_{max}$. The normal ventilatory reserve is 20% to 40% of the MVV or at least 15 L/min. A low breathing reserve during exercise is usually indicative of ventilatory limitations. Patients

with moderate to severe chronic airflow obstruction typically have low or no breathing reserve at the end of incremental exercise (Ruppel, 2003).

VENTILATION-PERFUSION (V/Q): The ventilation/perfusion ratio (or V/Q ratio) is a measurement used to assess the efficiency and adequacy of the matching of two variables where “V" (ventilation) equals the air which reaches the lungs and “Q" (perfusion) equals the blood which reaches the lungs. These two variables constitute the main determinants of the blood oxygen concentration. In fact, since “V” determines the quantity of oxygen mass reaching the alveoli per minute (g/min) and “Q” expresses the flow of blood in the lungs (L/min), the V/Q ratio refers to a concentration (g/l) (van der Graff & Fox, 1992).

VITAL CAPACITY (VC): The maximal volume of air that can be exhaled following a maximal inspiration (Ruppel, 2003).

-FORCED VITAL CAPACITY (FVC): The maximum volume of air moved when the subject tries to expire as forcefully and rapidly as possible, after a maximal inspiration (Ruppel, 2003).

-FORCED EXPIRATORY VOLUME IN ONE SECOND (FEV_1): The volume of air expired in one second measured at the beginning of the FVC maneuver (Ruppel, 2003).

-FORCED EXPIRATORY VOLUME IN ONE SECOND (FEV_1)/ FORCED VITAL CAPACITY (FVC): The volume of air expired in one second from the beginning of the FVC maneuver divided by maximum volume of air that can be expired after a maximal inspiration (Ruppel, 2003).

General Terms

AEROBIC EXERCISE: Refers to exercise that involves or improves oxygen consumption by the body. Aerobic means "with oxygen", and refers to the use of oxygen in the body's metabolic or energy-generating process. Many types of exercise are aerobic, and by definition are performed at moderate levels of intensity for extended periods of time. To obtain the best results, an aerobic exercise session involves a warming up period, followed by at least 20 minutes of moderate to intense exercise involving large muscle groups, and a cooling down period at the end (ACSM, 2000).

ALPHA: Refers to the probability of making a Type I error (rejecting the null hypothesis when the null hypothesis is true).

ANALYSIS OF VARIANCE (ANOVA): A collection of statistical models, and their associated procedures, in which the observed variance is partitioned into components due to different explanatory variables.

BICYCLE ERGOMETER: A stationary bicycle, with varying degrees of resistance, used to measure the amount of work being done during a graded exercise test (ACSM, 2000).

BODY MASS INDEX (BMI): A measure of body fat that is based on height and weight.

BONFERRONI CORRECTION: A multiple-comparison correction used when several dependent or independent statistical tests are being performed simultaneously in order to avoid spurious positives. As such, the alpha value is lowered to adjust for the number of comparisons being performed (Aicken & Gensler, 1996).

BONFERRONI POST-HOC ANALYSIS: The Bonferroni simply calculates a new pairwise alpha to keep the familywise alpha value at .05 (or another specified value).

The Bonferroni is probably the most commonly used post hoc test, because it is highly flexible, very simple to compute, and can be used with any type of statistical test (Aickin & Gensler, 1996).

BOX M TEST: Box's M statistic is used to test for homogeneity of covariance matrices (SPSS, 2008)

CALIBRATION: A validation of specific measurement techniques and equipment.

CARDIOVASCULAR DISEASE: Refers to the class of diseases that involve the heart or blood vessels (arteries and veins).

CENTRAL NERVOUS SYSTEM: A part of the nervous system that functions to coordinate the activity of all parts of the body.

CIRCULATORY SYSTEM: An organ system that moves nutrients, gases and wastes to and from cells to help fight diseases and help stabilize body temperature and pH to maintain homeostasis. The main components of the human circulatory system are the heart, the blood and the blood vessels. The circulatory system includes the pulmonary circulation, a "loop" through the lungs where blood is oxygenated and the systemic circulation, a "loop" through the rest of the body to provide oxygenated blood. An average adult contains five to six quarts (roughly 4.7 to 5.7 liters) of blood, which consists of plasma, red blood cells, white blood cells, and platelets. Also, the digestive system works with the circulatory system to provide the nutrients the system needs to keep the heart pumping (van der Graff & Fox, 1992).

COVARIATE: A variable that is related to the dependent variable(s), which the researcher can not manipulate, but wants to remove its relationship from the dependent variable(s) before measuring differences in the independent variable(s) (SPSS, 2008).

DEPENDENT VARIABLE: The observed variable in an experiment or study whose changes are determined by the presence or degree of one or more independent variables.

EXERCISE PRESCRIPTION: A detailed exercise program designed specifically for an individual to improve his/her fitness level while reducing the risk of injury (ACSM, 2000).

GRADED EXERCISE TEST (GXT): The collection and analysis of expired gas during a graded exercise test provides a noninvasive means of obtaining metabolic variables such as $\dot{V}\mathrm{E}_{\max}$, RR, $\dot{V}\mathrm{O}_{2\max}$, RER, $\dot{V}\mathrm{E}_{\max}/\dot{V}\mathrm{O}_2$ and $\dot{V}\mathrm{E}_{\max}/\dot{V}\mathrm{CO}_2$.

INFORMED CONSENT: A process in which a person learns key facts about a clinical trial, including potential risks and benefits, before deciding whether or not to participate in a study. This form must be signed by the subject prior to conducting any study-related tests.

LEVENE'S TEST OF EQUALITY OF ERROR VARIANCE**:** Levene's test for homogeneity of variances is typically used to confirm homoscedasticity (SPSS, 2008).

LONGITUDINAL STUDY: A longitudinal study is a correlational research study that involves repeated observations of the same items over long periods of time, often many decades. It is a type of observational study. Longitudinal studies are often used in psychology to study developmental trends across the life span. The reason for this is that unlike cross-sectional studies, longitudinal studies track the same people, and therefore the differences observed in those people are less likely to be the result of cultural differences across generations.

MEAN: The arithmetic average of a set of values.

MULTIPLE ANALYSIS OF COVARIANCE (MANCOVA): An extended form of the multiple analysis of variance (MANOVA) methods to cover cases where there is more than one (correlated) dependent variable and one or more independent variables and where the researcher wants to control for covariates. As well as identifying whether changes in the independent variables have a significant effect on the dependent variables, the technique also seeks to identify the interactions among the independent variables and the association among dependent variables, if any (SPSS, 2008).

MULTIVARIATE: Describes a collection of procedures involving observation and analysis of more than one statistical variable at a time. The word *multivariate* is defined as having or involving a number of independent mathematical or statistical variables.

NULL HYPOTHESIS: A statistical hypothesis about a population parameter. The purpose of hypothesis testing is to test the viability of the null hypothesis in the light of experimental data. Depending on the data, the null hypothesis either will or will not be rejected as a viable possibility (Aickin & Gensler, 1996).

OXYGEN PULSE (O_2 PULSE): A physiological term for oxygen uptake per heartbeat.

PANDEMIC: An epidemic of infectious disease that spreads through populations across a large region, i.e., a continent, or worldwide.

P-VALUE: The probability, with a value ranging from 0 to 1, of obtaining a result at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. The fact that p-values are based on this assumption is crucial to their correct interpretation.

QUADRICEPS: A large muscle group that includes the four prevailing muscles on the front of the thigh. It is the great extensor muscle of the knee, forming a large fleshy mass

which covers the front and sides of the femur. It is the strongest and leanest muscle in the human body.

RESISTANCE TRAINING: A form of strength training in which each effort is performed against a specific opposing force generated by resistance (i.e. resistance to being pushed, squeezed, stretched or bent). Exercises are isotonic if a body part is moving against the force. Exercises are isometric if a body part is holding still against the force. Resistance exercise is used to develop the strength and size of skeletal muscles (ACSM, 2000).

SEDENTARY: Refers to not being physically active.

STANDARD DEVIATION: A simple measure of the variability or dispersion of a data set. A low standard deviation indicates that all of the data points are very close to the same value (the mean); the high standard deviation indicates that the data are "spread out" over a large range of values (Aickin & Gensler, 1996).

WILK'S LAMBDA: A test statistic used in multivariate analysis of variance (MANOVA) to test whether there are differences between the means of identified groups of subjects on a combination of dependent variables. It is s a direct measure of the proportion of variance in the combination of dependent variables that is unaccounted for by the independent variable. If a large proportion of the variance is accounted for by the independent variable then it suggests that there is an effect from the grouping variable and that the groups have different mean values (SPSS, 2008).

WORKLOAD (WL): Refers to the incremental amount of work per unit of time (ACSM, 2000).

CHAPTER TWO: REVIEW OF RELATED LITERATURE

Overview

The acquired immune deficiency syndrome (AIDS) has emerged as a global pandemic over the past 28 years. Its etiologic agent, human immunodeficiency virus (HIV), is a blood-borne retrovirus commonly transmitted through sexual intercourse, parental inoculation, prenatal mother-to-infant transmission, blood transfusions, or during breast-feeding (WHO, 2000). There are two major subtypes of HIV currently recognized: HIV-1 and HIV-2. Further subdivisions can be made based on the sequence data of the virus (Roberson, Hahn & Sharp, 1995). Worldwide, the predominant virus is HIV-1 while HIV-2 is only prevalent in Western Africa. Both types of HIV have the same modes of transmission and both are precursors to clinically indistinguishable AIDS. HIV-1 and HIV-2 trigger the body to produce antibodies within three to six months, although the period between initial infection and illness may be longer in the case of HIV-2. The Centers for Disease Control and Prevention (CDC) utilize the following disease staging system to categorize the progression of HIV disease:

- **Stage A**: HIV-seropositive asymptomatic - testing positive for the HIV antibody while displaying no symptoms of a compromised immune system with a $CD4^+$ T-cell count of $\geq$ 500 cells/μL. Common symptoms at this stage of the disease include asymptomatic HIV-infection, acute primary HIV-infection with accompanying illnesses and persistent swollen lymph nodes (CDC, 1993).

- **Stage B**: HIV-seropositive symptomatic conditions - testing positive for the HIV antibody while beginning to display early symptoms of a compromised immune system with a $CD4^+$ T-cell count $\geq$ 200 but < 500 cells/μL (CDC, 1993).
- **Stage C**: AIDS indicator conditions - the disease has progressed to such a state that $CD4^+$ T-cells have decreased to < 200 cells/μL and the patient becomes susceptible to a variety of opportunistic infections and systemic disorders. A patient meets the clinical case definition of AIDS if their $CD4^+$ T-cell count is < 200 cells/μL, even if they do not display any opportunistic infections (CDC, 1993).

Lung impairment has been documented at the onset of HIV infection (Miller, 1996). This has been substantiated by the observation that HIV-1 sequences have been found in pulmonary cell populations recovered from the respiratory tracts of HIV-1 seropositive subjects at all stages of infection (Ong, 1997). In fact, stage B ($CD4^+$ T-cells $\geq$ 200 but < 500 cells/μL) is the phase of HIV-1 disease where many respiratory complications begin to manifest. Patients at this juncture have reached a transitional stage during which progression to advanced HIV-1 disease may be imminent and the risk of severe HIV-associated pulmonary infections are expected to increase substantially.

With the advent of new and more efficacious drugs designed to retain lean body mass and bolster immune function, many more HIV-1 seropositive patients are living longer, returning to normal activities of daily living and exercising. This includes aerobic or cardiovascular exercise as well as resistance training. However, it is unknown if one form of exercise is more beneficial than the other for improving the quality of life for someone living with HIV/AIDS. The purpose of this study was to determine if there

were any significant differences in resting and exercising pulmonary function among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men. This chapter will be divided into the following:

- Structure and Function of the Healthy Lung and its Relationship to the Respiratory System
- Obstructive Lung Disease in HIV-1 Seropositives
- Restrictive Lung Disease in HIV-1 Seropositives
- Modulation of Resting Pulmonary Function Tests in HIV-1 Seropositives
- Modulation of Exercising Pulmonary Function Tests in HIV-1 Seropositives

Structure and Function of the Healthy Lung and its Relationship to the Respiratory System

The human lungs occupy a large portion of the chest cavity from the collarbone down to the diaphragm. The diaphragm is a dome-shaped sheet of muscle separating the chest cavity from the abdominal cavity (van der Graff & Fox, 1992). Each lung is approximately 25 to 30 centimeters (cm) long, weighs roughly one pound each and is conical (van der Graff & Fox, 1992). The functional structure of the lung can be divided into the conducting airways (dead space) and the gas exchange regions (alveoli). The anatomical divisions of the conducting airways include the trachea, bronchi, bronchioles, terminal bronchioles and alveolar ducts.

The lungs are a pair of elastic, spongy organs critical for respiration and gas exchange. Gas exchange by the lungs is accomplished by a well-coordinated interaction of the lungs with the central nervous system, diaphragm, chest wall musculature and circulatory

system. The respiratory and circulatory systems work in tandem to deliver oxygen (O_2) to cells and remove carbon dioxide (CO_2) in a two-phase process called respiration. The first phase of respiration begins with inhalation or the process of breathing in O_2 (van der Graff & Fox, 1992). Inhalation transports air from outside the body into the lungs. Oxygen from the ambient air moves from the lungs to blood vessels of the heart, which then pumps the oxygen-rich blood to bodily tissues and cells completing the first phase of respiration. In the cells, O_2 is used in a separate energy-producing process called cellular respiration, which produces CO_2 as a byproduct. The second phase of respiration begins with the movement of CO_2 from the cells to the bloodstream in an attempt to reduce CO_2 in the body (van der Graff, K.M, et al., 1992). The bloodstream carries CO_2 to the heart, which pumps the CO_2-laden blood to the lungs, thus completing the second phase of the respiration cycle.

The organs of the respiratory system extend from the nose to the lungs and are divided into the upper and lower respiratory tracts. The upper respiratory tract consists of the nose and the pharynx. In addition, the mouth plays a supportive role to the constituents of the upper respiratory tract. The flow of air from outside the body into the lungs begins with the nose, which is divided into the left and right nasal passages. While transporting air to the pharynx, the nasal passages play two critical roles: they filter the air to remove potential disease-causing particles and they moisten and warm the air to protect the structures in the respiratory system. As air moves over the extensive capillaries in the nasal passages, the blood in the capillaries warms it. If the nose is blocked or "stuffy" due to a cold or allergies, a person is forced to breath through the mouth. This can be potentially harmful to the respiratory system membranes and potentially dangerous to

immunocompromised individuals, since the mouth does not filter, warm, or moisten air (van der Graff & Fox, 1992).

Air leaves the nasal passages and flows to the pharynx, a short, funnel-shaped tube about 13 cm long that transports air to the larynx. Like the nasal passages, the pharynx is lined with a protective mucous membrane and ciliated cells that remove impurities from the air. Air moves from the pharynx to the structures of the lower respiratory tract. The lower respiratory tract includes the larynx and the trachea, which splits into two main branches called the bronchi. From the pharynx, air passes through a structure about five cm long located in the middle of the neck called the larynx. Air then passes from the larynx into the trachea, a tube about 12 to 15 cm long located just below the larynx. The trachea is formed by 15 to 20 C-shaped rings of cartilage (van der Graff & Fox, 1992). The sturdy cartilage rings hold the trachea open, enabling air to pass freely at all times. The trachea divides into two branches (the right and left bronchi or bronchial tubes) that enter the lungs. The lung is composed of alveoli that number about 150 million per lung and comprise most of the lung tissue (van der Graff & Fox, 1992). Alveoli resemble tiny, collapsed balloons with thin elastic walls that expand as air flows into them and collapse when air is exhaled. At the alveoli, there is an intimate association with a vast capillary network that allows gas exchange as well as other metabolic functions to occur. Each alveolus is surrounded by many tiny capillaries, which receive blood from arteries and empty into veins. The exchange of gases takes place when air reaches the alveoli in a process known as diffusion. Since the concentration of O_2 is much higher in the alveoli than in the capillaries, the oxygen diffuses from the alveoli to the capillaries (van der Graff & Fox, 1992). The O_2 flows through the capillaries to larger vessels, which carry

the oxygenated blood to the heart where it is then pumped to the rest of the body. The CO_2 that has diffused into the bloodstream as a waste product flows to the heart and then to the alveolar capillaries. As a result, the concentration of CO_2 in the capillaries becomes much higher than in the alveoli, causing the CO_2 to diffuse into the alveoli. Exhalation forces the carbon dioxide back through the respiratory passages and outside the body (van der Graff & Fox, 1992).

Interspersed among the alveoli are numerous macrophages (large white blood cells) that patrol the alveoli and remove foreign substances that have not been filtered out earlier. The macrophages are the last line of defense of the respiratory system. The cilia of the larger airways and macrophages together dispose of entrapped infectious materials (van der Graff & Fox, 1992). Their presence helps to protect the alveoli from infection so that they are able to perform their vital role in gas exchange.

The amount of air normally taken into the lungs in a single breath during quiet breathing is called the tidal volume (V_T). In healthy adults, the V_T is equal to about 0.5 liters. The lungs can hold about ten times this volume when they are filled to capacity. This maximum amount of air that can be exhaled, termed vital capacity (VC), is generally about 4.8 liters in a healthy adult male, however it may vary among different groups of people. Athletes can have a VC as high as 5.7 liters (van der Graff & Fox, 1992), which may only be attained during strenuous exercise. An adult normally breathes from 14 to 20 times per minute. However, during vigorous exercise, this can reach a respiratory rate (RR) of up to 80 breaths per minute (Fox, Bowers & Fox, 1993). The V_T multiplied by the RR is equivalent to the minute ventilation (V_E) or the amount of air expired per minute. This is known to increase 20-fold during strenuous exercise.

In HIV-1 seropositive patients, lung volumes are often lower than in healthy adults as the lungs are principle targets of the infectious and noninfectious complications of the virus (Martin and Criner, 1999). The lungs become a microenvironment where viral replication readily occurs in response to a host of local factors. Excessive immune activity in the lung results in structural and functional damage thereby increasing the incidence of lung dysfunction. In fact, 80% of AIDS patients die from respiratory failure of which 90% of these cases are infectious (CDC, 1993). The lung disorders reported in HIV/AIDS patients can be categorized into either/or obstructive and restrictive lung disease. As the spectrum of pulmonary diseases associated with HIV continues to broaden, it becomes increasingly important to define the types of lung impairments most commonly found in HIV-infected individuals.

Obstructive Lung Disease in HIV-1 Seropositives

Obstructive lung disease occurs as a result of recurrent upper respiratory tract infections (URTI), i.e., acute asthma, chronic influenza and chronic sinusitis. In obstructive lung disease, airway obstruction causes an increase in resistance to airflow. The most common causes of airway obstruction in HIV-1 disease include inflammation of the airways, degeneration of the airways due to infection and damage to the tracheobronchial tree caused by aggressive immune responses (Wallace, Stone, Browdy, Tashkin, Hopewell, Glassroth, Rosen, Reichman & Kvale, 1997). As a result, the pressure-volume relationship of the diseased lung is altered. The pressure-volume relationship of the lung is related to the amount of force necessary for the inspiratory muscles to overcome the elastic and resistive properties of the respiratory system in order to increase and/or decrease lung volume and generate airflow within the lung.

During quiet breathing (rest) there is no difference in the pressure-volume relationship between the normal lung and the diseased lung. The work of breathing is performed entirely by the inspiratory muscles while expiration is passive. However, this situation changes during exercise. When breathing rapidly, i.e., during exercise, greater pressure (ΔP) is needed to overcome the resistance to flow during expiration and the volume (ΔV) of each breath gets smaller. As a result, patients with obstructive lung disease display reductions in expiratory flow rates. The reduction in expiratory airflow may be the result of a decrease in airway diameter and an increase in airway resistance or the obliteration of lung tissue and loss of airway structural support, causing reduced elastic recoil of the lungs during expiration (Ferguson & Cherniak, 1993).

Changes in elastic recoil may alter the amount of air that is moved with each respiratory effort leading to decreases in expiratory flow rates such as the forced vital capacity (FVC) (Westphal, 1994). The FVC is either normal or reduced depending on the severity of airflow obstruction (Criner & D'Alonzo, 1999). Furthermore, the ratio of forced expiratory volume in one second (FEV_1) to the total FVC (FEV_1/FVC) is much lower than normal, i.e., 40% as opposed to 80%. Patients with asthma, chronic bronchitis, and emphysema (all common in HIV-1 patients) demonstrate a decrease in rates of expiratory airflow, which may be manifested by a decrease in FVC and in FEV_1/FVC (Crapo, 1994). This may indicate air being trapped due to the closure of airways during forced expiration. The closure of the diseased airway during expiration is directly related to the inability of the lung to exert the necessary change in pressure (ΔP) needed to overcome resistance to flow in the narrowed airways during rapid breathing

(Altose, 1979). As a result, it is very difficult for a person with obstructive lung disease, i.e., asthma, to exhale quickly due to the increase in airway resistance.

The most common symptom of obstructive lung disease is dyspnea (breathlessness), which subsequently leads to exercise limitations. During exercise, patients with airflow obstruction are considerably more dyspneic than normals for comparative levels of work and ventilation (Killian & Campbell, 1983). In fact, patients with obstructive lung disease, usually display breathlessness as a limiting factor to their exercise (Jones & Campbell, 1982). The patient with obstructive lung disease may have impairment in either ventilatory capacity (decreased ability to increase V_E during exercise) or ventilatory requirement (increased V_E to oxygenate the blood and eliminate CO_2, thereby preventing excess CO_2 accumulation) (Gallagher, 1997).

Increases in V_E during progressive exercise can be achieved by increasing either V_T or RR. In the healthy population, V_T increases first followed by increases in RR in early exercise. This breathing pattern increases alveolar ventilation, which enhances breathing efficiency during early exercise. During incremental peak exercise, V_T plateaus as it approaches 60% of VC. As a result, the healthy subject begins to ventilate more rapidly to achieve a $\dot{V}E_{max}$ of 60 to 80% of maximum voluntary ventilation (MVV) at peak exercise. Although MVV is measured at rest, the maneuver mimics the work of active breathing during maximal exercise and is, therefore, a useful index in predicting ventilatory reserve during maximal exercise. In healthy subjects, there is a substantial ventilatory reserve (20 to 40%) at peak exercise indicating that peak exercise is not limited by the ability to maximally ventilate the lungs.

In patients with airflow obstruction, increases in V_E are achieved primarily by increases in RR during early exercise (Marciniuk & Gallagher, 1994) rather than by increased V_T. This compromises alveolar ventilation and, hence, breathing efficiency. During incremental peak exercise, $\dot{V}E_{max}$ approaches or equals MVV indicating a lack of ventilatory reserve and a ventilatory limitation to exercise. In patients with obstructive lung disease, MVV is typically reduced either directly from increased airway hyperresponsiveness or from fixed airflow obstruction that causes a decline in airway conductance during the MVV maneuver (Hallstrand, Bates & Schoene, 2000). As a result, the compromised breathing efficiency and lack of ventilatory reserve can lead to early termination of the graded exercise test (GXT) at a limited workload (Stringer, 2000).

In addition, many obstructive lung disorders are characterized by a mismatch of the ventilation-perfusion (V/Q) ratio. A V/Q ratio of one is reflective of normal gas exchange. A decrease in the V/Q ratio is indicative of little or no ventilation in the lung and rarely occurs in clinical medicine (D'Alonzo, 1999). In HIV-1 disease, a high V/Q ratio (greater than one) is often observed. This indicates an increase in the ratio of wasted ventilation that does not result in oxygen delivery to the working tissues. This wasted ventilation is termed dead space ventilation, V_D, and is often related to structural and functional damage to the lung parenchyma and alveoli from chronic immunologic responses causing a rise in the V_D/V_T ratio (Martin & Criner, 1999). Consequently, a high V_D/V_T is directly related to high V/Q. This is reflective of reduced gas exchange as is commonly seen in early pulmonary infection (Stringer, 2000). Typically the V_D/V_T represents approximately 33% of the V_T and actually decreases during moderate

submaximal exercise (Stringer, 2000). In contrast, progressive HIV-1 disease results in no change or an actual increase in the V_D/V_T ratio during moderate submaximal exercise. As dead space and wasted ventilation increase, so does V_T and the work of breathing. This leads to an increased ventilatory requirement for exercise and an exercise limitation with dyspnea.

In asymptomatic and early symptomatic HIV-1 seropositive patients, the damage caused to the lung by recurrent URTIs, i.e., colds, flu, asthma, etc, and the impending immune responses are the primary causes of obstructive lung disease. In fact, chronic recurrent URTIs are responsible for the majority of opportunistic infections that lead to obstructive lung disease (Wallace, et al., 1997). On average, HIV-1 seropositive patients experience up to 45% more URTIs in a 1-year period than a comparative healthy population (O'Donnell, et al., 1988). As a result, HIV-1 seropositives typically have reduced resting FVC, FEV_1, FEV_1 /FVC, peak expiratory flow (PEF) and MVV.

In a prospective cohort study of 1,116 HIV-1 seropositive patients, URTI was the most common diagnosis each year, ranging from 35 – 52 episodes per person with 33% reporting at least one URTI during the study period (Wallace, et al., 1997). A study by O'Donnell, et al., 1988, examined the airway function of 99 HIV/AIDS patients and found that 44% had low forced expiratory flow rates as a result of acute bouts of asthma. Symptomatic chronic sinus disease affects as many as 16% of HIV-1 patients and is especially common among those with advanced HIV disease (Miller, 1996). These startling statistics suggest that URTIs are among the leading indications for lung dysfunction and deterioration in HIV-1 disease.

As HIV-1 disease progresses, it inhibits the ability of the immune system to produce immunoglobulin A (IgA), an antibody that is responsible for attacking foreign pathogens in the upper respiratory tract of the lungs (Reynolds, 1997; Reynolds, 1988). As a result, HIV-1 patients become more susceptible to opportunistic pathogens entering the body via the air passages. Following intense exercise, IgA production is suppressed for up to two days (Nieman & Nehlsen-Cannarella, 1992) thereby increasing the incidence of URTI in healthy athletes. Studies have reported an increase in URTI immediately following intense exercise training in healthy athletes due to suppressed immune function. Interestingly, there are no studies examining the incidence rates of URTI following acute or chronic exercise or the effects of URTI on pulmonary function values in HIV-1 seropositive patients. However, the implications from these studies should be considered when prescribing an exercise program for persons with HIV-1 disease. Since HIV-1 patients have a higher incidence of URTI and experience some degree of compromised immunity, it is important to prescribe an exercise program that will allow for an improved exercise training effect while minimizing the negative and acute effect of exercise on their immune function.

Restrictive Lung Disease in HIV-1 Seropositives

Restrictive lung disease occurs as a result of recurrent lower respiratory tract infections (LRTI), i.e., pneumocystis carinii pneumonia, interstitial pneumonia, bronchitis, and pulmonary edema. In restrictive lung disease, the compliance of the lung is reduced, which increases the stiffness of the lung and limits expansion. In these cases, a greater change in pressure difference (ΔP) is required to provide the same increase in volume (ΔV) (Altose, 1979). Common causes of decreased lung compliance commonly

seen in HIV/AIDS patients include pulmonary fibrosis, pneumonia and pulmonary edema. Restrictive lung disease is characterized by a decrease in inspiratory lung volumes due to a reduction in lung compliance (stiff lungs) while expiratory airflow remains normal (Murray & Mills, 1990). The VC is reduced, whereas the FEV_1/FVC is normal (Weinberger, 1998). The FVC is smaller than normal, but the FEV_1 is relatively large in comparison, i.e., the FEV_1/FVC ratio can be higher than normal, for example 90% as opposed to 80%. This is because it is easy for a person with a restricted lung (i.e., pulmonary fibrosis) to breathe out quickly due to the high elastic recoil of the stiff lung.

At any given level of ventilation, V_T is decreased and breathing frequency is increased (Lama & Martinez, 2004). The increased respiratory frequency is caused by reductions in both inspiratory and expiratory time (Javaheri & Sicilian, 1992). The breathing pattern mimics external elastic loading, suggesting that mechanoreceptors and increased lung recoil contribute to the rapid, shallow breathing pattern (Tjahja, Reddy & Janicki, 1994). As a result, smaller breath-to-breath variations in V_T and expiratory time are seen in patients with restrictive lung disease and leads to marked increases in dyspnea with slight variations in V_T (Brack, Jubran & Tobin, 2002). Although the patient population has a small and limited inspiratory capacity (IC), there are sufficient increases in V_T as V_E rises. As a result, the ratio of V_T/IC increases similarly between restricted and control subjects. However, the restricted subject's rapid, shallow breathing pattern results in hypoxemia, hypercapnia and severe dyspnea at low workloads (Tjahja, et al., 1994). The lack of increase in the V_T during exercise contributes to a failure to decrease V_D/V_T (Lama & Martinez, 2004). As a result, at increased work rates, the increase in V_T/IC

ratio reflects a limited capacity to perform high level or maximum exercise indicated by an absolute level that is lower compared to controls. During peak exercise, the RR can compensate for the reduced V_T and IC by increasing in excess of 50 beats per minute (Murray & Mills, 1990).

In asymptomatic and early symptomatic HIV-1 seropositive patients, the damage caused to the lung by recurrent LRTI, i.e., interstitial lung disease, and the impending immune responses are the primary causes of restrictive lung disease. In fact, chronic recurrent LRTIs are responsible for the majority of opportunistic infections that lead to restrictive lung disease and are often an indication of the progression of HIV-1 disease (Clarke & Israel-Biet, 1998). On average, HIV-1 seropositive patients experience up to 52% more LRTIs in a 1-year period than in the healthy population (O'Donnell, et al., 1988). As a result, HIV-1 seropositives typically have a reduced FVC but normal or higher FEV_1, FEV_1 /FVC, PEF and MVV.

A 5-year retrospective study examining the respiratory trends in HIV/AIDS, found a steady increase (from 21 to 34 episodes per 100) in the number of newly diagnosed LRTIs during the study period (Wallace, Hansen, Lavange, Glassroth, Browdy, Rosen, Kvale, Mangura, Reichman & Hopewell, 1997). A study by Shaw, et al., 1988, examined the pulmonary function of 168 HIV/AIDS patients and found that 40% had experienced pulmonary complications, i.e. pneumonia. In fact, pneumonia accounted for 84% of the LRTIs. Symptomatic chronic bronchitis was reported to affect as many as 21% of HIV-1 patients and is especially common among those with advanced HIV-1 disease (Miller, 1996). These statistics suggest that LRTIs are one of the leading indications for lung dysfunction and deterioration in HIV-1 disease. The frequent and recurrent bouts of

LRTIs in HIV-1 disease lead to a constant, but futile, attempt of the immune system to defend the lung against a myriad of microbial agents. The interactions between HIV and infectious agents in the lung are harmful to the lung itself, and, as result, could enhance the progression of HIV-1 disease (Clarke & Israel-Biet, 1998).

As HIV-1 disease progresses, it inhibits the ability of the immune system to produce immunoglobulin G (IgG), an antibody that is responsible for attacking foreign pathogens in the lower respiratory tract of the lungs (Reynolds, 1991; Reynolds, 1987). The lack of IgG in the lower respiratory tract and the damage to the lung caused by intense immune responses makes the lung a prime target for opportunistic infections (Reynolds, 1997). Nieman & Nehlsen-Cannarella (1992) examined the effects of chronic exercise on immunoglobulins in healthy athletes. This study demonstrated serum IgG levels were suppressed for up to two days. Consequently, a smaller amount of serum IgG diffused into the airways and alveolar space secretions in response to microbial agents and antigens introduced into the airways during the exercise bout, increasing the incidence of LRTI.

Given the higher incidence of LRTI in seropositives, it is somewhat surprising that there are no studies examining the incidence rates of LRTI following acute or chronic exercise. However, the implications from these studies should be considered when prescribing an exercise program for persons with HIV-1 disease. The implications from these studies are that a temporary immunosuppression may occur acutely in the post-exercise period, which may leave seropositives particularly vulnerable to LRTIs as well as URTIs during this time. Thus, it is important for HIV-1^{+} patients to follow an exercise

program that will improve exercise tolerance and capacity while minimizing the potential negative effects on their immune function.

Modulation of Resting Pulmonary Function Tests in HIV-1 Seropositives

Spirometric tests are commonly utilized at rest to evaluate mechanical function of the airways, lung parenchyma and subsequent functional impairment of the lungs of apparently healthy as well as diseased populations (Basson & Stewart, 1991). HIV-1 seropositive patients may be tested to assess symptoms such as chronic cough, dyspnea (Rosen, et al., 1995) and impairment of lung function (Pothoff, et al., 1994). The use of these tests is further substantiated by Wiedemann (1991) who found that spirometric and lung volume measurements estimate mechanical function of the airways and lung parenchyma. The major role of these tests in HIV-1 patients is to aid in the selection of symptomatic patients with normal or near-normal chest x-rays who have abnormalities on PFTs that require further diagnostic evaluations (West, 1997). Negative results from PFTs should be used in concert with other resting and exercising PFTs to determine the extent and nature of the limitation.

There are two types of functional disturbances that have been detected on PFTs in the early symptomatic HIV-1 population (White & Stover, 1996). These include an obstructive ventilatory defect characterized by low FVC and FEV_1 values (Shaw, et al., 1988) and a restrictive ventilatory defect characterized by a low V_T and IC (Zurlo, 1997). The limitations in expiratory flow rates are commonly observed in HIV-1 early symptomatic patients (Stage B). Shaw and his colleagues, 1988, conducted a study on lung function abnormalities during the course of HIV-1 disease and found that early

symptomatic, HIV-1 seropositive subjects had normal FEV_1, PEF and FVC, however, PEF was at the lower end of the normal range (92% of predicted). Furthermore, an 18-month cohort study tracking respiratory disease trends in HIV-1 disease, found that although early symptomatic HIV-1 seropositive subjects showed no significant decline in lung function for FEV_1 and PEF, during this stage of the disease (Mitchell, et al., 1992), their reported scores were still at the lower end of the normal range (90% of predicted). Rosen and her colleagues (1995) found similar results in which no significant differences were observed in resting mean FVC, FEV_1 and FEV_1/FVC between seropositive and seronegative subjects. However, 10.4% and 12.1% of seropositive subjects tested below the 95% prediction limit for FVC and FEV_1, respectively. This suggests that there is a precipitous decrease in lung capacity at the early stages of the disease. Furthermore, a study conducted at the University of Miami's Center for Exercise Medicine recorded significantly lower resting pulmonary function variables (FVC, FEV_1, PEF, MVV and VC) for HIV-1 seropositives compared to controls (Talluto, et al., 1999). It is important to note that some or all of the resting lung function values were at the lower end of the normal range. This may be an early indication of mechanical lung dysfunction. A study by Schulz and her colleagues (1997) demonstrated a decrease in respiratory muscle strength in HIV-1 disease. This could account for the abnormally low expiratory flow rates commonly seen in HIV-1 disease (Shaw, et al., 1988; O'Donnell, et al., 1988). A study by O'Donnell, et al., 1988, reported 42% of patients with AIDS had abnormal airway function which may be indicative of obstructive lung disease and/or a mixed ventilatory defect (Libman & Witzburg, 1990).

Recently, a large cohort study of 1,353 individuals, either HIV-1 seropositive or at high risk for HIV-infection, were stratified according to peripheral CD4 lymphocyte count and were followed up by an 18-month period. The results were as follows: 33.4% reported upper respiratory infection, 16% had an episode of acute bronchitis and 5.3% an episode of acute sinusitis and bacterial pneumonia occurred in 4.8% (Wallace, Rao & Glassworth, 1993). A similar 5-year cohort study conducted by Wallace and her research team on the respiratory disease trends of people infected with HIV-1 disease demonstrated a greater incidence of URTI and LRTI in patients infected with HIV-1 disease, regardless of the stage of disease. These studies demonstrate that people infected with HIV-1 disease suffer from a myriad of opportunistic infections that contribute to obstructive and/or restrictive lung disease at any stage of HIV-1 disease.

Modulation of Exercising Pulmonary Function Tests in HIV-1 Seropositives

In diseased populations, exercise testing can be helpful when resting lung function tests are inconclusive or indicate intermediate degrees of impairment. Exercise testing can also be used when the patient's symptoms are discordant with the results of resting lung function tests (Wiedemann, 1991). Several mechanisms for exercise limitation can be observed in HIV-1 seropositive patients including ventilatory, pulmonary, vascular and peripheral muscle de-conditioning (Klemack, 2007; Stringer, et al., 1998; Stringer, 2000).

A study by Johnson and his researchers (1990) compared the results of cardio-pulmonary fitness testing between a group of 32 HIV-1 seropositive men (Stages A-C, mean age 28) and a similar group of seronegative controls to determine the presence of

exercise dysfunction in HIV-1 disease. Both groups reported participating regularly in an aerobic exercise program. Subjects performed a $\dot{V}O_{2\ max}$ test on an electromechanically braked bicycle ergometer using an incremental GXT protocol. At rest, there were no significant differences in heart rate (HR), $\dot{V}E_{\ max}$ or RR between the HIV-1 seropositives and the controls. During the GXT, however, the HIV-1 seropositive group exercised to a significantly lower workload at a similar maximum HR compared to controls. The $\dot{V}O_{2\ max}$ and $\dot{V}E_{\ max}$ were numerically but not significantly lower in the HIV-1 seropositive group. This is suggestive of a limited exercise capacity in this population. A study by Talluto, et al., 1999, compared exercising lung function between HIV-1 seropositives and seronegatives during a maximum GXT. The 4 groups included aerobically-trained, HIV-1 seropositives (n=10), sedentary, HIV-1 seropositives (n=10), aerobically-trained, HIV-1 seronegatives (n=10) and sedentary, HIV-1 seronegatives (n=10) between the ages of 18 and 45. The aerobically-trained, HIV-1 seropositives reported significantly lower values in exercising lung function at maximum work rates including dyspnea index (DI), V_D/V_T and O_2 pulse compared to a matched group of HIV-1 seronegatives. Sedentary, HIV-1 seropositives also showed significantly lower $\dot{V}E_{\ max}$, $\dot{V}O_{2\,max}$, $\dot{V}CO_2$ and O_2 pulse at maximal exercise when compared to aerobically-trained, HIV-1 seropositives. This suggests that aerobic exercise training may be associated with enhanced exercise capacity concomitant with increased exercising lung function in HIV-1 seropositives. These results were in agreement with those reported by Pothoff et al., 1994, evaluating the exercise capacity of 75 HIV-1 seropositive patients during various stages of the disease. The first group consisted of 20 patients without a history of respiratory disease and without actual lung disease. The

second group consisted of 18 patients that experienced one broncho-pulmonary complication without actual lung disease while the last group consisted of 37 patients with different broncho-pulmonary complications. The control group consisted of 20 seronegative subjects with no history of respiratory disease. Results indicated significantly lower values in exercise capacity at $\dot{V}O_{2\,max}$ and O_2 pulse for the three heterogeneous groups of HIV/AIDS patients when compared to the HIV-1 seronegative controls. The more advanced stages of HIV/AIDS resulted in an even greater reduction in exercising lung function.

Similar to aerobic exercise, there have been a limited number of resistance-training studies conducted on HIV/AIDS patients. Studies by Lox, et al., 1995, Rigsby, et al., 1992 and Spence, et al., 1990 have demonstrated that resistance-training programs have had positive effects on HIV-1 seropositive patients including significant increases in body weight, lean body tissue and strength. Consequently, resistance-training programs may also increase respiratory muscle strength. Increases in respiratory muscle strength would be extremely beneficial to HIV-1 patients since previous research has demonstrated a decrease in respiratory muscle function due to obstructive and restrictive lung disease associated with the progression of HIV-1 disease (Schulz, et al., 1997). Unfortunately, to date, there are no published studies on the effects of resistance training on resting or exercising lung function.

The present study examined the effects of previous exercise training on resting and exercising pulmonary function in active seropositives as compared to sedentary seropositives. Previous research has not compared resting and exercising pulmonary function in HIV-1 seropositives engaging in cardiovascular and resistance training

programs. It is possible that the HIV population can participate in a regular exercise program and as a result, experience similar training effects as the "apparently healthy" population. Exercise training has been shown to improve the quality of life of those infected and may possibly aid in slowing down the progression of the disease itself (Stringer, 2000). Therefore, it may be relevant to conduct research evaluating the effects of previous aerobic and resistance training on resting and exercising pulmonary function in patients with HIV-1 disease.

Summary

The primary function of the lung is rapid gas exchange. However, in HIV-1 disease, this process becomes impaired and, as a result, affects the respiratory capacity of HIV-1 patients. HIV-1 infected individuals have compromised immune systems and are extremely susceptible to the development of URTI and LRTI with a variety of organisms, most of which are rarely seen in individuals with normal immune systems. As a result, the increased frequency of pulmonary infections in HIV-infected populations contributes to their decreased lung function values at rest and during exercise (Zurlo, 1997).

As the scope of HIV-related pulmonary complications continues to broaden, it becomes increasingly important to determine the most prevalent types of lung impairment associated with HIV-1 disease. The two main categories of HIV-related pulmonary disease are obstructive lung disease and restrictive lung disease. In obstructive lung disease, airway obstruction causes an increase in resistance to airflow. As a result, patients with obstructive lung disease often display reduced expiratory flow rates and dyspnea. In restrictive lung disease, the compliance of the lung is reduced, which increases the stiffness of the lung and limits expansion. As a result, patients with

restrictive lung disease often experience decreases in inspiratory flow volumes due to a reduction in lung compliance while expiratory airflow remains normal.

PFTs are used to aid in the selection of symptomatic patients with normal or near-normal chest x-rays who demonstrate abnormalities on PFTs that require further diagnostic evaluations. Several research studies reported decreased resting pulmonary function values for HIV-1 seropositives when compared to a similar group of seronegatives suggesting a precipitous attenuation in lung capacity in HIV-1 disease.

Exercise testing is helpful when resting PFTs are inconclusive or when the patient's symptoms are discordant with the results of resting PFTs. Previous research has reported decreased maximum exercise capacity concomitant with reduced exercising lung function values in HIV-1 seropositives when compared to a similar group of seronegatives. Also, sedentary HIV-1 seropositives have reported decreased maximum exercise capacity when compared to aerobically-trained HIV-1 seropositives suggesting that aerobic exercise training may result in enhanced exercise capacity concomitant with enhanced exercising lung function during maximum exercise. Additionally, there are no studies to date that have evaluated either resting or exercising pulmonary lung function values in seropositives who perform resistance training.

The present study examined the effects of previous exercise training on resting and exercising pulmonary function in active HIV-1 infected individuals as compared to sedentary, seropositive controls. This is extremely important since lung function is often compromised before the onset of any major illnesses in HIV-1 disease. Thus, this study will determine whether seropositives who exercise on a regular basis show a higher level

of pulmonary function, both at rest and during exercise, and ultimately greater respiratory health than those who are sedentary.

CHAPTER THREE: METHODS AND PROCEDURES

The purpose of this study was to determine if there were any significant differences in resting and exercising pulmonary function among sedentary, resistance-trained and aerobically-trained, early symptomatic, human immunodeficiency virus (HIV) -1 seropositive men.

Sample

This study included 15 sedentary, 15 resistance-trained and 15 aerobically-trained, early symptomatic HIV-1 seropositive men between the ages of 18 and 45. Subjects were recruited from prior studies conducted by the Behavioral Medicine Research Center and via flyers posted in local HIV/acquired immunodeficiency syndrome (AIDS) organizations and health clubs. Potential subjects completed a screening telephone questionnaire (Appendix A) to determine preliminary eligibility. The telephone questionnaire evaluated the subject's medical history, smoking habits and current exercise program. During the telephone interview, subjects were excluded from participating in this study if they reported a previous diagnosis of any AIDS-defining symptoms, i.e., $CD4^+$ T-cell count < 200 cells/μL, any pre-existing medical conditions, i.e., asthma, hypertension, cardiovascular disease, obstructive or restrictive lung disease, smoking tobacco within the past six months or active participation in both aerobic and weight-training programs within the past six months.

Upon meeting the initial criteria for acceptance during the telephone interview, the subject was invited into the laboratory to perform additional screening procedures. Subjects were instructed to bring a letter from their physician confirming their HIV-1 serostatus, disease classification, most recent T-cell count and permission to participate in this study. Prior to commencing any procedures, a written informed consent form

(Appendix B) was obtained in accordance with the procedures set forth by the University of Miami's Human Subjects Institutional Review Board. During the informed consent process, potential subjects were instructed to carefully read the informed consent form and encouraged to ask questions to ensure that they had a thorough understanding of the study.

After subjects signed the informed consent form, their current exercise programs, if any, were reviewed to ensure that there were no significant changes since the initial telephone interview. Each subject's current exercise program was evaluated based on the American College of Sports Medicine (ACSM) guidelines for frequency, duration and intensity of exercise. Subjects who reported no physical activity on a regular basis within the past six months were considered to be sedentary and met the minimal criteria for participating in this study in the inactive sedentary group. Subjects who reported participating in a resistance-training program working every major muscle group for a minimum of three days per week for the past six months met the initial criteria for participating in this study in the resistance-training group. Subjects who reported participating in an aerobic-training program for a minimum of three days per week, for a minimum of 30 minutes per session, within the past six months, met the initial criteria for participating in this study in the aerobically active group.

Once the preliminary groups were established based on self-reported exercise programs, the subjects were further evaluated using spirometric testing to evaluate resting pulmonary function and a graded exercise test (GXT) to evaluate aerobic fitness group. During the spirometric testing, subjects were required to complete three trials for the forced expiration maneuver and two trials for the hyperventilation maneuver. Subjects who completed the two breathing maneuvers, as instructed, were allowed to continue in the study and were prepped for the GXT. Guidelines for subjects' aerobic fitness were based upon their peak $\dot{V}O_2$ obtained during a GXT as categorized by ACSM accordingly (Table 1).

Table 1: American College of Sports Medicine Aerobic Fitness Classification

Age (Yrs.)	Low	Fair	Average	Good	High
18-29	< 25	25-33	34-42	43-52	≥ 53
30-39	< 23	23-30	31-38	39-48	≥ 49
40-49	< 20	20-36	27-35	36-44	≥ 45

Maximal $\dot{V}$O2 values reported in ml/kg/min

Subjects who scored average, fair or low on the GXT and who did not engage in any type of regular exercise program within the past six months were placed in the sedentary inactive group. Subjects who scored average, fair or low on the GXT and who participated in a resistance-training program only within the past six months were placed in the resistance-training group. Two subjects who reported active participation in a resistance-training program were excluded from the study since they also scored good or high for aerobic fitness during the GXT. Subjects who scored good or high on the GXT and who participated in an aerobic exercise program only within the past six months were placed in the aerobically active group. Four subjects who reported active participation in an aerobic-training program were excluded from the study since they scored average, fair or low for aerobic fitness during the GXT. A total of six out of 51 subjects were excluded from the study based upon ACSM guidelines for the GXT.

Resting Pulmonary Function Measures

The Sensor Medics® 2130 computerized spirometer, which was used to assess all measures of resting pulmonary function, was calibrated prior to each test (Sensor Medics, 1992). The calibration procedure involved connecting a three-liter positive displacement calibration syringe that was operated manually to generate a volume change using a push/pull mechanism. The push/pull mechanism was performed for six complete, consecutive inspire/expire strokes. The computer program was corrected for the

appropriate volumes and then applied a correction factor to adjust the calibration curve to a linear flow curve. The procedure was performed two times to ensure the spirometer was calibrated correctly. The correction factor between the two calibration procedures was required to fall within 0.9 and 1.2 liters or the calibration procedures were repeated. Each subject performed three tests in an upright position, breathing into a disposable, microbacterial filtered mouthpiece while wearing a disposable nose clip.

Measures of expiration included forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). The procedure for measuring FVC and FEV_1, required the subject to insert the mouthpiece into their mouth, with nose clip in place, breathe quietly for five tidal breaths, then inspire maximally to total lung capacity (TLC), followed by a maximum forced expiration performed as rapidly as possible for a minimum of six seconds. The subject was required to perform three trials and the results from two of the trials were required to be within 10% to ensure the reproducibility and validity of each maneuver as established by the American Thoracic Society (ATS) guidelines (1994). If the results varied by more than 10%, the subject was asked to repeat the maneuver. The subject was allowed to repeat the maneuver up to two additional times.

An additional measure used to assess the subject's ability to rapidly and forcefully expire air was the maximum voluntary ventilation (MVV). To measure MVV, the subject was required to insert the mouthpiece into the mouth with nose clip in place and breathe as deeply and rapidly as possible for 12 seconds. The value obtained during the 12-second maneuver was multiplied by five to extrapolate the results to one minute (West, 1997). Two trials were performed with the highest value recorded as established

by ATS guidelines (1994). If trial results varied by more than 10%, the subject was asked to repeat the maneuver to ensure better reproducibility and reliability of each maneuver (Hankinson & Bang, 1991). The subject was allowed to repeat the maneuver up to two additional times.

Exercising Pulmonary Function Measures

The Sensor Medics® 2900C Metabolic Measurement Cart was used to assess aerobic fitness and other metabolic variables as well as ventilatory and gas exchange variables. Calibration procedures were performed prior to each test once the metabolic cart had reached operating temperature (Sensor Medics, 1992). The flowmeter was calibrated using a three-liter positive displacement calibration syringe which is manually operated to generate a square-wave volume change. The computer program corrects the calibrating piston volumes for the current barometric pressure and temperature and applies a correction factor to adjust the calibration curve to the linear flow curve. Calibration of the analyzer involved automatic adjustment of the analyzer so the measured output was equivalent to the known input of the calibration gases. The calibration gas concentrations were pre-entered in the computer and when the measured concentrations did not equal the known concentrations, correction factors were applied. The correction factors were then utilized to adjust all the oxygen (O_2) and carbon dioxide (CO_2) readings throughout the GXT.

A Hans Rudolph, one-way valve mouthpiece was used to collect gases during each test. A fully automated electrically braked cycle ergometer SensorMedics® Ergoline 800 was used for all GXTs. Prior to the start of the GXT, subjects were seated on the bicycle for two minutes. A standard bicycle ergometer protocol was used in which the subject pedaled at a power output of 25 watts for the first two minutes, followed by an increase of 25 watts every two minutes until the subject was unable to continue pedaling the bike

at a predetermined cadence of 60 revolutions per minute (ACSM, 2000). The test was terminated when one or more of the following criteria for achieving peak $\dot{V}O_2$ were met:

- the subject displayed a plateau or decrease in peak $\dot{V}O_2$ with increasing workload
- the subject displayed a respiratory exchange ratio above 1.15
- the subject reduced the cadence despite urging by the testing staff (volitional exhaustion) (Fox, et al., 1989)

Upon completion of the GXT, subjects were instructed to continue riding the bicycle at a slow pace until their heart rates had returned to their pre-testing heart rate (PHR).

The rating of perceived exertion and blood pressure were recorded at the start of the test, during the last 60 s of each two-minute stage, and when the subject was unable to continue pedaling the bike at the predetermined cadence.

Heart rates were recorded using a 12-lead stress ECG MAX1 (Marquette Electronics, Inc.) interfaced with the metabolic cart. Subjects were prepared for the electrocardiogram (ECG) by abrading and cleansing the area where electrodes were to be placed. The electrodes were positioned as follows: right infraclavicular notch (RA), left infraclavicular notch (LA), right side, midway between the lowest rib and suprailiac crest (RL), left side, midway between the lowest rib and the suprailiac crest (LL), right, fourth intercostal space (V1), left, fourth intercostal space (V2), midway between V2 and V4 (V3), anterior axillary line, fifth intercostal space (V5) and midaxillary line, fifth intercostal space (V6). The corresponding leads were then attached to the electrodes and the unit was secured around the subject's waist. Heart rates were measured prior to the test, continuously during the GXT and continuously after the test until the subject returned to their PHR.

Exercising pulmonary function included metabolic, ventilatory and gas exchange measures, evaluated during the GXT. The only metabolic measure collected during the GXT was peak $\dot{V}O_2$. The ventilatory measures collected during the GXT included maximum minute ventilation ($\dot{V}E_{max}$), shortness of breath known as the dyspnea index (DI = $\dot{V}E_{max}$/MVV x 100), dead space to tidal volume ratio (V_D/V_T) and RR as a function of $\dot{V}E_{max}$ ($RR/\dot{V}E_{max}$). The only gas exchange measure collected during the GXT was the ventilatory equivalent for CO_2 ($\dot{V}E_{max}/\dot{V}CO_2$).

Although, the meaning and limitation of each measurement can be considered individually, the integrated use of all the variables collected during the GXT provides a more powerful diagnostic tool. Furthermore, resting measures of pulmonary function coupled with an assessment of metabolic, ventilatory and gas exchange measures provide a comprehensive evaluation of one's pulmonary status and capacity to perform work. An integrated summary of these measurements may help to gain a more complete understanding of the exercise limitations seen in HIV-1 seropositive patients with obstructive lung disease, restrictive lung disease or a mixed ventilatory defect.

Statistical Analysis

Variables were assessed using univariate procedures to summarize the characteristics of the study population [reported as means ± standard deviation (SD)]. An analysis of variance (ANOVA) was conducted to assess group differences in physical characteristics (age, height, weight, body mass index (BMI) and average years diagnosed HIV-1 seropositive). Levene's test of the error variance on the dependent variables was

conducted to check the assumption that the error variance of the dependent variable was equal across groups.

Prior to conducting a multiple analysis of co-variance (MANCOVA) test for the resting pulmonary function variables, a Box M test was used to test the homogeneity of the variance/covariance matrix among three matrices. In addition, Levene's Test of Equality of Error Variances was employed to check the assumption that the error variance of the dependent variables was equal across groups. A MANCOVA, covarying for age, BMI and the average years diagnosed HIV-1^{+}, with one between-subjects factor (fitness level), was used to analyze the resting pulmonary function variables which included FVC, FEV_1, FEV_1/FVC and MVV. When significant differences were observed, Bonferroni post-hoc comparisons were performed to analyze the source of significance among the groups. When significant differences were observed for a primary variable, that null hypothesis was rejected. Likewise, when no significant differences were observed for a primary variable, that null hypothesis was accepted. All levels of significance were set at ≤ 0.05 (Hair, Black, Babin, Anderson, & Tathan,, 2006).

Prior to conducting a multiple analysis of co-variance (MANCOVA) test for the exercising pulmonary function variables, a Box M test was used to test the homogeneity of the variance/covariance matrix among three matrices. In addition, Levene's Test of Equality of Error Variances was employed in order to check the assumption that the error variance of the dependent variables was equal across groups. A MANCOVA, co-varying for age, BMI and the average years diagnosed HIV-1^{+}, with one between-subjects factor (fitness level), was used to analyze the exercising pulmonary function variables from the GXT which included $\dot{V}E_{max}$, peak $\dot{V}O_2$, DI, V_D/V_T, $\dot{V}E_{max}/\dot{V}CO_2$ and $RR/\dot{V}E_{max}$.

When significant differences were observed, Bonferroni post-hoc comparisons were performed to analyze the source of significance among the groups. When significant differences were observed for a primary variable, that null hypothesis was rejected. Likewise, when no significant differences were observed for a primary variable, that null hypothesis was accepted. All levels of significance were set at ≤ 0.05 (Hair, et al., 2006).

CHAPTER FOUR: RESULTS

The purpose of this study was to determine if there were any significant differences in resting and exercising pulmonary function among sedentary, resistance-trained and aerobically-trained, early symptomatic, human immunodeficiency virus (HIV)-1 seropositive men.

A total of 45 HIV-1 seropositive men participated in this study. The subjects were divided into the following three groups: sedentary (n=15), resistance-trained (n=15) and aerobically-trained (n=15). All subjects signed an informed consent form, completed a medical history and physical activity questionnaire and underwent the following assessments: resting pulmonary function tests (PFTs) and a graded exercise test (GXT).

The mean (±SD) age, height, weight, body mass index (BMI) and average years diagnosed HIV-1^+ for each group are presented in Table 2.

Table 2: Analysis of Variance (F) of Subject Characteristics by Group

Variable	Sedentary M ± SD	Resistance M ± SD	Aerobic M ± SD	F	P-Value
Age (yrs.)	34.6 ± 6.6	28.4 ± 7.0[a]	34.7 ± 5.1	5.14	.010
Height (cm)	175.3 ± 6.1	173.2 ± 6.3	177.4 ± 2.8	1.56	.222
Weight (kg)	81.8 ± 8.0[b]	75.3 ± 5.9	75.9 ± 9.6	4.84	.013
BMI (kg^2/m)	26.4 ± 1.5[b]	25.11 ± 1.7	24.1 ± 1.2	9.50	.001
Average Yrs. HIV-1^+	6.2 ± 1.9[c]	5.13 ± 2.9	3.8 ± 1.9	4.78	.013

M = Mean, SD = standard deviation

[a] Statistically significant from the sedentary and aerobically-trained groups, $p < 0.05$

[b] Statistically significant from the resistance and aerobically-trained groups, $p < 0.05$

[c] Statistically significant from the aerobically-trained group, $p < 0.05$

An analysis of variance (ANOVA) was conducted to assess group differences for physical characteristics (age, height, weight, BMI and average years diagnosed HIV-1^+).

Levene's test revealed error variance of the dependent variables was equal across groups, p-values ranged from 0.068 to 0.846. ANOVA results revealed that there were statistically significant differences among groups for age ($F_{2, 42} = 5.14$, $p<0.01$), weight ($F_{2, 42} = 4.84$, $p<0.013$), BMI ($F_{2, 42} = 9.50$, $p<0.001$) and average years HIV-1^{+} ($F_{2, 42} = 4.78$, $p<0.013$).

Post-hoc comparisons of physical characteristics were conducted among groups, using the Bonferroni correction to the alpha level (p, 0.05/5 variables = 0.01) on each dependent variable as a follow-up to the ANOVA test. Bonferroni post-hoc pairwise comparisons showed that the resistance-trained group was significantly younger than the sedentary ($p<0.024$) and aerobically-trained groups ($p<0.025$). There was no significant difference in age between the sedentary and aerobically-trained groups. The sedentary group also weighed more than the resistance ($p<0.021$) and aerobically-trained groups ($p<0.045$) with no significant difference in weight between the resistance and aerobically-trained groups. Furthermore, the sedentary group also had a significantly higher BMI than both the resistance ($p<0.03$) and aerobically-trained groups ($p<0.01$) with no significant difference in BMI between the resistance and aerobically-trained groups. Again, the sedentary group was diagnosed with HIV-1 significantly longer than the aerobically-trained group ($p<0.011$) with no significant differences in the average number of years diagnosed with HIV-1 between the sedentary and resistance-trained groups or between the resistance and aerobically-trained groups.

Resting Pulmonary Function Measures

All resting pulmonary function variables were sufficiently correlated with each other (r ranged from .309 to .850, p = 0.05) to justify the use of Multiple Analysis of Covariance (MANCOVA) for this data set. MANCOVA, controlling for age, BMI and average years HIV-1^{+}, with one between subjects factor (fitness level), was conducted to

assess group differences in resting pulmonary function among groups. The Box M test was not significant indicating the observed covariance matrices of the dependent variables were equal across groups: Box M = F (20, 6331) = 3.338, p = 0.20. Levene's test revealed that the error variance of the dependent variables was equal across groups, p-values ranged from 0.255 to 0.878. MANCOVA results revealed statistically significant differences among the three groups, Wilks' $\lambda = .310$, F (8, 72) = 7.164, p = 0.001, multivariate $\eta^2 = .443$. None of the covariates influenced the combined dependent variables in the model for resting pulmonary function.

As a follow-up to the MANCOVA, univariate ANOVAs were conducted and are presented in Table 3.

Table 3: ANOVA of Resting Pulmonary Function in Sedentary, Resistance and Aerobically-Trained, Early Symptomatic, HIV-1^+ Men

Variable	Sedentary M ± SD	Resistance M ± SD	Aerobic M ± SD	F	P-Value	Partial η^2
FVC (L)	4.4 ± .43	4.7 ± .35	5.3 ± .37[a]	8.53	.001	.304
FEV_1 (L)	3.4 ± .38	4.1 ± .43[b]	4.7 ± .38[a]	15.50	.001	.443
FEV_1/FVC (%)	0.8 ± .05	0.9 ± .08[b]	0.9 ± .05[b]	4.69	.015	.194
MVV (L)	117.8 ± 13	137.3 ± 16.7	170.3 ± 16.8[a]	17.97	.001	.480

η2 = eta squared

[a] Statistically significant from the sedentary and resistance trained groups, $p < 0.05$

[b] Statistically significant from the sedentary group, $p < 0.05$

ANOVA showed significant between-group differences in forced vital capacity (FVC) ($F_2 = 8.53$, P = .001), forced expiratory volume in one second (FEV_1) ($F_2 = 15.50$, P = .001), the ratio of FEV_1/FVC ($F_2 = 4.69$, P = .015) and maximum voluntary ventilation (MVV) (($F_2 = 17.97$, P = .001).

Post-hoc comparisons of resting pulmonary function were conducted among groups, using the Bonferroni correction to the alpha level (p, 0.05/4 variables = 0.0125) (Aickin

& Gensler, 1996) on each dependent variable, as a follow-up to the ANOVA test. Bonferroni post-hoc pairwise comparisons showed that the aerobically-trained group attained significantly higher FVC values than the sedentary and resistance-trained groups ($p<0.01$) with no significant differences in FVC values between the sedentary and resistance-trained groups. The aerobically-trained group also attained significantly higher FEV_1 values than the sedentary ($p<0.01$) and resistance-trained groups ($p<0.05$). In addition, the resistance-trained group reported significantly higher FEV_1 values than the sedentary group ($p<0.023$). In addition, further evaluations of FEV_1/FVC showed that the aerobically-trained group attained significantly higher FEV_1/FVC values than the sedentary group ($p<0.004$). The resistance-trained group also reported significantly higher FEV_1/FVC values than the sedentary group ($P<0.038$). There was no difference in FEV_1/FVC values between the resistance and aerobically-trained groups. Further evaluations of MVV revealed that the aerobically-trained group attained significantly higher MVV values than the sedentary and resistance-trained groups ($p<0.01$) with no significant differences in MVV values between the sedentary and resistance-trained groups.

Exercising Pulmonary Function Measures

All exercising pulmonary function variables were sufficiently correlated with each other (r ranged from .387 to .749, $P = 0.01$) to justify the use of MANCOVA for this data set. A MANCOVA, controlling for age, BMI and average years HIV-1^+, with one between subjects factor (fitness level), was conducted to assess group differences in exercising pulmonary function among fitness groups. The Box M test was not significant

indicating the observed covariance matrices of the dependent variables were equal across groups: Box M = F (42, 5236) = 1.429, p = 0.162. Levene's test revealed error variance of the dependent variables was equal across groups, p-values ranged from 0.069 to 0.83. MANCOVA results revealed statistically significant differences among the three groups, Wilks' $\lambda = .095$, F (12, 68) = 12.68, p = 0.001, multivariate $\eta^2 = .692$. None of the covariates influenced the combined dependent variables in the model for exercise pulmonary function.

As a follow-up to the MANCOVA, univariate ANOVAs were conducted and are presented in Table 4.

Table 4: ANOVA of Exercise Pulmonary Function in Sedentary, Resistance and Aerobically-Trained, Early Symptomatic, HIV-1^+ Men

Variable	Sedentary M ± SD	Resistance M ± SD	Aerobic M ± SD	F	P-Value	Partial η^2
$\dot{V}E_{max}$ (l/min)	108.9 ± 16.7	123.4 ± 16.7	149.5 ±13.3[a]	13.52	.001	.410
$\dot{V}O_2$ (ml/kg/min)	25.2 ± 1.9	30.5 ± 1.9[b]	41.4 ± 3.2[a]	111.89	.001	.852
DI (%)	0.81 ± .19	0.78 ± .12	1.04 ± .12[a]	9.00	.001	.316
V_D/V_T (%)	0.13 ± .02	0.11 ± .02[b]	0.08 ± .02[a]	20.86	.001	.517
$\dot{V}E_{max}/\dot{V}CO_2$ (%)	0.56 ± .09	0.54 ± .15	0.55 ± .09	0.22	.803	.011
$RR/\dot{V}E_{max}$ (%)	0.55 ± .11	0.41 ± .05[b]	0.34 ± .06[a]	17.13	.001	.468

[a] Statistically significant from the sedentary and resistance trained groups, $p < 0.05$
[b] Statistically significant from the sedentary group, $p < 0.05$

ANOVA showed significant between-group differences in maximum minute ventilation ($\dot{V}E_{max}$) ($F_2 = 13.52$, P = .001), peak O_2 uptake (peak $\dot{V}O_2$) ($F_2 = 111.89$, P = .001), dyspnea index (DI) ($F_2 = 9.00$, P = .001), dead space to tidal volume ratio (V_D/V_T) ($F_2 = 20.86$, P = .001) and respiratory rate (RR) as a function of $\dot{V}E_{max}$ ($RR/\dot{V}E_{max}$) ($F_2 = 17.13$, P = .001).

Post-hoc comparisons of exercising pulmonary function were conducted among groups, using the Bonferroni correction to the alpha level (p, 0.05/6 variables = 0.0083) (Aickin & Gensler, 1996) on each dependent variable as a follow-up to the univariate ANOVA test. Bonferroni post-hoc pairwise comparisons showed that the aerobically-trained group attained significantly higher $\dot{V}E_{max}$ values than the sedentary and resistance-trained groups ($p<0.01$) with no significant differences in $\dot{V}E_{max}$ values between the sedentary and resistance-trained groups. The aerobically-trained group also attained significantly higher peak $\dot{V}O_2$ values than the sedentary and resistance-trained groups ($p<0.01$). In addition, the resistance-trained group reported significantly higher peak $\dot{V}O_2$ values than the sedentary group ($p<0.01$). Furthermore, the aerobically-trained group also attained significantly higher DI values than the sedentary ($p<0.03$) and resistance-trained groups ($p<0.01$) with no difference in DI values between the sedentary and resistance-trained groups. The aerobically-trained group also attained significantly lower V_D/V_T values than the sedentary and resistance-trained groups ($p<0.01$). In addition, the resistance-trained group reported significantly lower V_D/V_T values than the sedentary group ($p<0.019$). Finally, the aerobically-trained group attained significantly lower $RR/\dot{V}E_{max}$ values than the sedentary ($p<0.01$) and resistance-trained groups ($p<0.05$). In addition, the resistance-trained group reported significantly lower $RR/\dot{V}E_{max}$ values than the sedentary group ($p<0.001$).

Summary

There were significant differences in physical characteristics among the groups. The resistance-trained group was significantly younger than the sedentary and aerobically-trained groups and the sedentary group was significantly heavier and had a significantly

higher BMI than the resistance and aerobically-trained groups. The sedentary groups had also been diagnosed with HIV-1 disease significantly longer than the other two groups. These differences did not influence the MANCOVA for either resting or exercising pulmonary function.

For resting pulmonary function, the main effect showed significant differences among the dependent variables. Further analysis using univariate ANOVA and Bonferroni post-hoc comparisons showed that the aerobically-trained group had significantly higher FVC, FEV_1 and MVV values than both the sedentary and resistance-trained groups and a significantly higher FEV_1/FVC ratio than the sedentary group.

For exercising pulmonary function, the main effect also showed significant differences among the dependent variables. Further analysis using univariate ANOVA and Bonferroni post-hoc comparisons showed that the aerobically-trained group had significantly higher $\dot{V}E_{max}$, peak $\dot{V}O_2$ and DI values than both the sedentary and resistance-trained groups. The aerobically-trained group also showed significantly lower V_D/V_T and $RR/\dot{V}E_{max}$ values than the other two groups. The resistance-trained groups also showed a significantly higher peak $\dot{V}O_2$ value and significantly lower V_D/V_T and $RR/\dot{V}E_{max}$ value than the sedentary group.

CHAPTER FIVE: DISCUSSION AND CONCLUSIONS

Overview

The purpose of this study was to determine if there were any significant differences in resting and exercising pulmonary function among sedentary, resistance-trained and aerobically-trained, early symptomatic, human immunodeficiency virus (HIV)-1 seropositive men. This study included 15 sedentary, 15 resistance-trained and 15 aerobically-trained, early symptomatic HIV-1 seropositive men between the ages of 18 and 45. Subjects who successfully completed all spirometric and graded exercise tests were included in the data analysis. The analysis examined differences in lung function values among sedentary, resistance-trained and aerobically-trained early symptomatic HIV-1 seropositive men at rest and during maximal exercise. An analysis of variance was conducted to assess group differences in physical characteristics (age, height, weight, body mass index (BMI) and average years diagnosed HIV-1^{+}). Multiple analyses of co-variance (MANCOVA) tests were performed to examine differences in resting and exercising pulmonary function variables among the three groups.

The following chapter will consist of (a) Summary of Findings, (b) Discussion and Applications, (c) Conclusions and their Significance and (d) Recommendations for Future Research.

Summary of Findings

1. Physical Characteristics: There were statistically significant differences among sedentary, resistance-trained and aerobically-trained groups in physical characteristics. Further analysis revealed these differences did not influence MANCOVA results for either resting or exercising pulmonary function.
    a. Age: The resistance-trained group was significantly younger than the sedentary and aerobically-trained groups. There were no significant differences in age between the sedentary and aerobically-trained groups.
    b. Weight: The sedentary group weighed significantly more than both the resistance and aerobically-trained groups. There were no significant differences in weight between the resistance and aerobically-trained groups.
    c. BMI: The sedentary group had a significantly higher BMI than both the resistance and aerobically-trained groups. There were no significant differences in BMI between the resistance and aerobically-trained groups.
    d. Average Years HIV-1 Seropositive: The sedentary group was diagnosed with HIV-1 significantly longer than the aerobically-trained group. There were no significant differences in the average number of years diagnosed with HIV-1 between the sedentary and resistance-trained group or between the resistance and aerobically-trained group.
2. Resting Pulmonary Function: There were statistically significant differences among the sedentary, resistance-trained and aerobically-trained groups in resting pulmonary function.

a. Forced Vital Capacity (FVC): The aerobically-trained group attained significantly higher FVC values than the sedentary and resistance-trained groups. There were no significant differences in FVC values between the sedentary and resistance-trained groups.

b. Forced Expiratory Volume in one second (FEV_1): The aerobically-trained group also attained significantly higher FEV_1 values than the sedentary and resistance-trained groups. In addition, the resistance-trained group evidenced significantly higher FEV_1 values than the sedentary group.

c. FEV_1/FVC: The aerobically-trained group attained significantly higher FEV_1/FVC values than the sedentary group. The resistance-trained group also evidenced significantly higher FEV_1/FVC values than the sedentary group. There was no difference in FEV_1/FVC values between the resistance and aerobically-trained groups.

d. Maximum Voluntary Ventilation (MVV): The aerobically-trained group attained significantly higher MVV values than the sedentary and resistance-trained groups. There were no significant differences in MVV values between the sedentary and resistance-trained groups.

3. Exercising Pulmonary Function: There were statistically significant differences among sedentary, resistance-trained and aerobically-trained groups in exercising pulmonary function.

a. Maximum Minute Ventilation ($\dot{V}E_{max}$): The aerobically-trained group attained significantly higher $\dot{V}E_{max}$ values than the sedentary and

resistance-trained groups. There were no significant differences in $\dot{V}E_{max}$ values between the sedentary and resistance-trained groups.

b. Peak O_2 uptake (peak $\dot{V}O_2$): The aerobically-trained group also attained significantly higher peak $\dot{V}O_2$ values than the sedentary and resistance-trained groups. The resistance-trained group reported significantly higher peak $\dot{V}O_2$ values than the sedentary group.

c. Dyspnea Index (DI): The aerobically-trained group also attained significantly higher DI values than the sedentary and resistance-trained groups. There were no differences in DI values between the sedentary and resistance-trained groups.

d. Dead Space to Tidal Volume ratio (V_D/V_T): The aerobically-trained group attained significantly lower V_D/V_T values than the sedentary and resistance-trained groups. The resistance-trained group also evidenced significantly lower V_D/V_T values than the sedentary group.

e. Ventilatory equivalent for carbon dioxide (CO_2) ($\dot{V}E_{max}/\dot{V}CO_2$): There were no significant differences among groups for $\dot{V}E_{max}/\dot{V}CO_2$

f. Respiratory Rate (RR) as a function of $\dot{V}E_{max}$ ($RR/\dot{V}E_{max}$): The aerobically-trained group attained significantly lower $RR/\dot{V}E_{max}$ values than sedentary and resistance-trained groups. The resistance-trained group evidenced significantly lower $RR/\dot{V}E_{max}$ values than the sedentary group.

Discussion and Application

The aerobically-trained group evidenced significantly higher FVC, FEV_1 and MVV values than the resistance-trained group and significantly higher FVC, FEV_1, FEV_1/FVC and MVV values than the sedentary group. In fact, the aerobically-trained group reported resting pulmonary function values consistent with an apparently healthy seronegative population reporting scores at or close to 100% of their predicted values (Barreiro & Perillo, 2004). This demonstrates that the aerobically-trained group was able to adequately and efficiently move air in and out of the lungs at rest with no signs of obstructive or restrictive lung impairment. The fact that the aerobically-trained group demonstrated a constellation of higher resting pulmonary function values than resistance-trained and sedentary seropositives suggests that regular aerobic exercise may be helpful in maintaining normal resting pulmonary function and may help to delay the decline in pulmonary function commonly observed in HIV-1 disease. This will enable seropositive patients to continue to perform their normal activities of daily living and maintain a better standard of living for a longer period of time in comparison to sedentary or resistance-trained seropositives.

Although the resistance-trained group reported significantly lower FVC, FEV_1 and MVV values than the aerobically-trained group, they still evidenced significantly higher FEV_1 and FEV_1/FVC ratio in comparison to the sedentary group. This suggests that resistance training may provide some benefit in maintaining normal resting lung function in seropositive individuals, albeit to a lesser extent than the aerobically-trained group. The resistance-trained group reported FEV_1 scores consistent with that of healthy seronegatives (approximately 90% of predicted) demonstrating an ability to forcefully

push air out of the lungs quickly during the first second of the maneuver. However, their decreased FVC and MVV values in comparison to aerobically-trained seropositives, as well as healthy seronegatives, showed an inability to sustain forceful and rapid exhalation maneuvers over an extended period of time indicating the onset of pulmonary complications at rest. This type of resting breathing pattern (reduced FVC but normal or high FEV_1/FVC ratio) is typical of HIV-related restrictive and obstructive ventilatory defects and is characterized by the loss of lung volume in the absence of airflow obstruction and possible lack of respiratory muscle strength (Rosen, et al., 1995). Although MVV values were 17% higher than the sedentary group, they were still significantly below that of the aerobically-trained seropositives. A reduced MVV is commonly observed in HIV-1 seropositive patients with moderate to severe obstruction as a result of increased airway resistance caused by bronchospasm or mucous secretion (Rabinovich, 2005). Thus, although the resistance-trained group showed better resting pulmonary function compared to the sedentary group, their values were not as favorable as aerobically-trained seropositives or seronegative controls suggesting some HIV-related pulmonary limitations at rest.

The sedentary group reported significantly reduced FVC, FEV_1, FEV_1/FVC ratio and MVV in comparison to the aerobically-trained group and significantly reduced FEV_1 and FEV_1/FVC ratio in comparison to the resistance-trained group. This signifies the decline in pulmonary function commonly observed in HIV-1 disease. In spite of reduced FVC and FEV_1, the sedentary group's FEV_1/FVC ratio was still within the lower limit of the normal range (approximately 80% of predicted). A normal FEV_1/FVC ratio, despite low FVC and FEV_1 values, is typical of restrictive lung impairment and is characterized by a

decrease in inspiratory lung volumes and a reduction in lung compliance and distensibility (Bradley, et al., 1976). This pattern is also indicative of a mixed ventilatory defect characterized by airflow obstruction as a consequence of airway closure resulting in gas trapping and reduced lung volumes (Majumdar, Sen & Mandal, 2007). The significant reduction in MVV compared to the aerobically-trained group, underscores the severity of lung impairment since the sedentary group had difficulty sustaining any type of rapid, forceful breathing maneuver at rest. Poor performance in pulmonary function tests by the sedentary group demonstrates an impaired ability to adequately and efficiently move air in and out of the lungs at rest These findings support the fact that sedentary patients infected with HIV-1 have a more progressive deterioration of their resting lung function relative to the two exercise groups thereby exacerbating the deleterious effects of HIV-1 disease. Differences in pulmonary function among the three groups at rest provide ammunition to support exercise in the amelioration of the destructive effects of HIV-1 disease.

The aerobically-trained group also evidenced significantly superior exercising pulmonary function values than both the resistance-trained and sedentary groups. For example, the aerobically-trained group evidenced significantly higher $\dot{V}\mathrm{E}_{\mathrm{max}}$ values demonstrating an ability to move larger volumes of air in and out of the lungs than the other two groups (Lumb, 2000). The aerobically-trained group also reported significantly higher peak $\dot{V}\mathrm{O}_2$ values in comparison to the resistance-trained and sedentary groups demonstrating a higher aerobic capacity and better efficiency in supplying adequate oxygen to the exercising muscles at higher workloads (Cordova, Kukafka & D'Alonzo, 1999). Furthermore, the aerobic group reported significant decreases in the ratios of

V_D/V_T and RR to $\dot{V}E_{max}$ resulting in lower cost of breathing and more efficient ventilation-perfusion in comparison to the resistance-trained and sedentary groups (Wasserman, 1992). Interestingly, the aerobic group also reported significantly higher DI scores than the other two groups but their greater windedness was likely due to the generation of greater workloads, a greater power output and a longer time on the graded exercise test. Thus, regular aerobic exercise is associated with better exercise capacity, resting and exercising lung function and may help to delay the deleterious effects of HIV-1 disease in resting and exercising lung function characteristic of early symptomatic seropositives.

Although the aerobic group evidenced significantly better exercising pulmonary function values than the other seropositive groups, several exercising pulmonary function variables may be considered somewhat impaired relative to healthy seronegatives. For example, $\dot{V}E_{max}$ values are generally observed at 60-80% of MVV in healthy seronegatives indicating a 20-40% ventilatory reserve range. In the aerobically-trained group, however, a $\dot{V}E_{max}$ of 88% of MVV was observed falling 8-28% below that of healthy seronegatives. As a result, the aerobically-trained group compensated for this ventilatory limitation with an increase in respiratory rate which was well above that observed in healthy seronegatives (Lumb, 2000). As such, mild lung disease may not reduce $\dot{V}O_{2\,max}$, but may reduce the ventilatory reserve that exists at peak exercise (Wiedemann, 1991). Consequently, the reduced ventilatory reserve, coupled with excessive respiratory rate and reduced tidal volume, may result in inefficient gas exchange. Thus, aerobically-trained seropositives evidenced greater dead space values, a greater breathing equivalent for expiring $\dot{V}CO_2$ and a higher respiratory rate to achieve

$\dot{V}E_{max}$ compared to healthy seronegatives. The increased cost of breathing is common in HIV-1 disease and is attributable to a higher energy expenditure and greater work output for a given volume of ventilation. Consequently, decreases in ventilation-perfusion are observed leading to hypoxemia and hypercapnia (Hsia, 1999). Thus although the aerobically-trained group showed pulmonary advantages compared to the other two groups, there were still signs of early stage pulmonary limitations and declining lung function associated with HIV-1 disease (Folgering & von Herwaarden, 1994).

The resistance-trained group reported exercising pulmonary function values somewhere between the aerobically-trained and sedentary groups suggesting a reduced exercise capacity and possible onset of HIV-related pulmonary impairment. However, the resistance-trained group evidenced significantly higher peak $\dot{V}O_2$ values and significantly lower dead space and respiratory rates necessary to achieve $\dot{V}E_{max}$ than the sedentary group. This suggests that the resistance-trained group was able to move a greater volume of air in and out of the lungs thereby supplying more oxygen to the working muscles at a lower cost of breathing in comparison to the sedentary group. Furthermore, the resistance-trained group also evidenced reductions in dead space resulting in better gas exchange efficiency compared to the sedentary group. More efficient gas exchange may be indicative of a healthier respiratory system and may lead to potential improvements in exercise capacity at greater workloads (Rabinovich, 2005). Thus, our findings suggest some beneficial pulmonary function values during exercise in the resistance-trained group. Although greater pulmonary function was observed during resting and exercising lung function compared to sedentary seropositives, they occurred to a lesser extent that that observed in the aerobically-trained group.

Similar to the aerobic group, the resistance-trained group showed substantial limitations to exercise compared to healthy seronegatives. For example, the resistance-trained group reported a $\dot{V}E_{max}$ that was 90% of MVV indicating only 10% ventilatory reserve, which is approximately 10-30% below that of healthy seronegatives. This suggests a ventilatory limitation to exercise when compared to healthy seronegatives. The resistance-trained group may have compensated for the aforementioned ventilatory difficulties by increasing breathing frequency as observed in the aerobically-trained group. They also evidenced significantly decreased tidal volume. Their inefficient breathing patterns contributed to increases in dead space and a greater respiratory rate to achieve $\dot{V}E_{max.}$ These results point to reductions in the ventilation-perfusion ratio and an inability to supply adequate oxygen to the working muscles at increased levels of work. Reduced gas exchange leads to hypoxemia and hypercapnia at lower workloads and reflects obstructive and/or restrictive pulmonary defects indicative of HIV-1 disease, regardless of training. Thus although exercising lung function was superior to sedentary seropositives, the resistance-trained group also displayed pulmonary limitations compared to aerobically-trained seropositives and healthy seronegatives.

The sedentary group reported the lowest exercising pulmonary function values of all three groups resulting in the lowest exercise capacity, the lowest ventilatory reserve, the highest dead space and cost of breathing and the most pronounced reductions in gas exchange. The sedentary group also evidenced significantly lower peak $\dot{V}O_2$ values and significantly higher dead space and respiratory rates necessary to achieve $\dot{V}E_{max}$ compared to both exercise groups. This suggests a low respiratory capacity and an inability to move sufficient amounts of air in and out of the lungs. As a result, this group

was unable to supply adequate oxygen to the working muscles. Furthermore, the sedentary group also evidenced increased dead space resulting in inefficient gas exchange compared to both exercise groups. Increases in metabolic energy requirements of compromised respiratory muscles can exceed 50% of available total oxygen delivery (Hsia, 1999). This compromises oxygen delivery to non-respiratory skeletal muscles involved in locomotion (Hsia, 1999). As such, reductions in exercise capacity may be attributable to both the deleterious effects of HIV-1 disease in the lung itself (Lipman, et al., 1997) and to the sedentary, de-conditioned status of subjects (Cade, Peralta & Keyser, 2004). This breathing pattern suggests more severe HIV-related pulmonary deterioration compared to both exercise groups. Our findings clearly demonstrate that both aerobic and resistance-trained groups displayed superior resting and exercising lung function values which may help to retard the progression of HIV-related pulmonary complications.

Given that the aerobically-trained group demonstrated the most favorable pulmonary function values suggests that aerobic exercise may be beneficial for maintaining normal lung function at rest and during work. Increased pulmonary demand during exercise serves to increase airflow to obstructed and restricted airways and may help to improve respiratory muscle endurance (Epstein & Celli, 1993). The fact that the resistance-trained group evidenced more favorable pulmonary function values than the sedentary group may be explained by their greater respiratory muscle strength which would decrease windedness and improve pulmonary function. (Folgering & von Herwaarden, 1994). Participation in regular aerobic or resistance-training exercise may also facilitate mucus removal and help maintain chest mobility (Folgering & von Herwaarden, 1994). Thus,

our findings lend support to recommending the implementation of regular exercise to assist HIV-1 seropositive patients in the maintenance of normal resting and exercising lung function. This is extremely relevant for seropositives who tend to show progressive deterioration of lung function in the long term.

There were several limitations that should be noted with respect to this study. First this was a cross-sectional study, thus differences among the groups were correlational, in nature, and may not necessarily be attributable to the longitudinal effects of training. The sedentary group was diagnosed with HIV-1 significantly longer than the two exercise groups which may have contributed to their significantly lower resting and exercising pulmonary function scores. It is well established that HIV-1 compromises pulmonary function even at the early stages of HIV-1 disease (Pothoff, et al., 1994). As such, the longer one has HIV-1 disease, the greater the available time for deleterious changes to occur in the lung (Mayaud & Cadranel, 1993). In addition, the sedentary group was significantly older, heavier and had a higher BMI than both aerobic and resistance-trained groups. The de-conditioning and subsequent excess weight may be a consequence of a more sedentary lifestyle exacerbating reductions in resting and exercising pulmonary function (Fox, et al., 1993).

This study was also limited in that it utilized patient-reported questionnaires to assess previous exercise training. It is possible that subjects did not accurately report the amount of exercise they performed during the six months prior to enrolling in this study. Furthermore, this study used effort-dependent tests to assess both resting and exercising pulmonary function. It is possible that sedentary individuals may have been unable or uncomfortable in pushing themselves to the same degree as those exercising on a regular

basis. In addition, the size for this study was small and, as such, these results may not translate to a larger group of early symptomatic HIV-1 seropositive men or those with more advanced HIV-1 disease. Finally, these results may not be extrapolated to early symptomatic HIV-1 seropositive females.

Conclusions

On the basis of this study, the following conclusions can be drawn:

1. The sedentary group evidenced resting and exercising pulmonary function scores consistent with restrictive lung disease and a mixed ventilatory defect.
2. The resistance-trained group reported resting and exercising pulmonary function scores consistent with obstructive lung disease and a possible mixed ventilatory defect.
3. The aerobically-trained group reported resting pulmonary function scores consistent with normal lung function.
4. The aerobically-trained group reported exercising pulmonary function scores consistent with a possible mixed ventilatory defect.
5. Participation in either aerobic or resistance training is associated with superior pulmonary function values above that of sedentary lifestyles.
6. Participation in a regular aerobic training program may be the most appropriate mode of exercise for maintaining pulmonary function status thereby delaying the onset of HIV-related pulmonary complications.

Based on the conclusions of this investigation:

Hypothesis # 1: There are no significant differences in resting pulmonary function values among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men. Hypothesis # 1 is rejected.

There were significant differences in resting pulmonary function values among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men. The significant differences occurred for all four resting pulmonary function variables (FVC, FEV_1, FEV_1/FVC and MVV).

Hypothesis # 2: There are no significant differences in maximum exercising pulmonary function values among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men. Hypothesis # 2 is rejected.

There were significant differences in maximum exercising pulmonary function values among sedentary, resistance-trained and aerobically-trained, early symptomatic, HIV-1 seropositive men. The significant differences occurred for $\dot{V}E_{max}$, peak $\dot{V}O_2$, DI, V_D/V_T and $RR/\dot{V}E_{max}$. There was no significant difference among groups in only one measure of exercise-related pulmonary function, $\dot{V}E_{max}/\dot{V}CO_2$.

Recommendations for Future Research

As a result of this study, the following recommendations for future research can be made:

1. Stratify the groups by the average number of years diagnosed with HIV-1 disease to determine the effects of different exercise regimens on lung function based on the length of time since diagnosis.

2. Stratify the groups by stage of disease to include asymptomatic, early symptomatic and acquired immunodeficiency syndrome (AIDS) defined patients to determine the effects of different exercise regimens on lung function as the disease progresses.
3. Ensure an equal distribution of subjects of males and females from diverse ethnic and socioeconomic backgrounds.
4. Ensure that future studies are conducted using a larger group of subjects.
5. Expand the present study to include participation in combination resistance and aerobic training programs which are more reflective of the current ACSM recommendations to determine which exercise program is the most beneficial for this patient population.
6. Examine a longitudinal rather than a cross-sectional exercise study to determine changes in pulmonary function status over time in HIV-1 seropositive patients.
7. Include body fat and lean body mass assessments during longitudinal exercise training to determine if resistance training, aerobic training or a combination both can be is beneficial in minimizing the effects of muscle wasting observed with HIV-1 disease.
8. Include hematology panels at designated times during a longitudinal exercise training study to determine the effects of exercise on immunological markers affected by HIV-1 disease.
9. Expand the present study to include more comprehensive lung function assessments including x-ray and body plethysmography in order to obtain a more

complete assessment of lung function including total lung capacity and residual volume.

10. Include assessments on the respiratory muscle group including maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) measurements to determine if different exercise regimens can improve respiratory muscle strength in HIV-1 seropositive patients.

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APPENDIX A: PRE-SCREENING QUESTIONNAIRE

UNIVERSITY OF MIAMI - SCHOOL OF MEDICINE
CENTER FOR EXERCISE MEDICINE
HIV-1 SEROPOSITIVE LUNG FUNCTION STUDY
SUBJECT ELIGIBLITY QUESTIONNAIRE

Subjects' Initials: _____

Date: _____

Address: _____

City/Zip Code: _____

Contact Telephone Number: _____

Alternate Telephone Number: _____

May we leave a detailed message about the study on your answering machine or with the person who may answer your telephone? _____

I am going to ask you a series of questions to get to know you better and to see if you are eligible to participate in this study. All your personal information will remain confidential.

What is your age? (must be between 18 and 50 years old) _____
What is your height? _____
What is your weight? _____
What is your racial/ethnic background? _____
What is the ethnicity of your father? _____
What is the ethnicity of your mother? _____
Are you HIV positive? _____
If yes, how long have you known you were positive? _____
Will you get a letter from your physician confirming your HIV status and provide a copy of your most recent blood work (must be within one month)?
_____

Do you know your current T-cell count? _____

I am going to read a list of HIV-related symptoms and I'd like you to tell me which of these, if any, that you have had? I am interested even if you've had one of these symptoms in passing or only once so I can look at changes in these symptoms? (If subject has had any of the symptoms, list the date and duration of the last occurrence and how often it has occurred.)

	Last date it occurred	Duration of last occurrence	Total # of episodes
Thrush	_____	_____	_____
Unintentional weight loss of > 10% or 15 pounds in last three months	_____	_____	_____
Herpes zoster (shingles) in last 5 yrs.	_____	_____	_____
Swollen lymph nodes (where?)	_____	_____	_____
Diarrhea (how often/day?)	_____	_____	_____
Oral hairy leukoplakia (white patches on tongue and mouth)?	_____	_____	_____
Chronic recurrent skin rash?	_____	_____	_____
Persistent fatigue w/in last 6 months interfering w/ normal activity?	_____	_____	_____
Night sweats?	_____	_____	_____
Fever of unexplained origin?	_____	_____	_____
Recurrent URTI?	_____	_____	_____
Muscle or joint pains?	_____	_____	_____
Unusual bruises, bumps or skin discoloration?	_____	_____	_____
Genital warts?	_____	_____	_____

Have you been diagnosed with any of the following? If yes, when?
(These are exclusionary.)

	Yes/No	Date of diagnosis
Chronic obstructive lung disease?	_____	_____
Restrictive lung disease?	_____	_____
Tuberculosis?	_____	_____

Diagnosis of AIDS?	_____	_____
Kaposi's sarcoma?	_____	_____
Lymphoma?	_____	_____
HIV wasting syndrome?	_____	_____
Pneumocystis Carinii Pneumonia (PCP)?	_____	_____
Toxoplasmosis of the brain?	_____	_____
Cytomegalovirus (CMV) of organ other than liver, spleen or or lymph nodes?	_____	_____
Herpes simplex virus infection more than 1 month in duration in the mucous membrane, i.e., esophagus, or viscera of any duration?	_____	_____
Progressive mutlifocal leukoencephalopathy (PML)?	_____	_____
Endemic mycosis?	_____	_____
Candidiasis of esophagus, trachea, bronchi or lungs?	_____	_____
Bedridden more than 50% of the day within the last month?	_____	_____
Cryptococcosis: cryptosporidiosis with diarrhea?	_____	_____
Thrombocytopenia (low platelets)?	_____	_____
T cell count < 200?	_____	_____

Do you currently smoke or have you smoked? _____
(Exclude anyone who smokes or has smoked)

Are you currently taking AZT or any other anti-retroviral drugs? _____

Medication	Date of Onset	Dosage	Duration
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

What other medications are you currently taking or have you taken within the last 3 months?

Medication	Date of Onset	Dosage	Duration
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

Have you had any type of infection within the last months? If yes, what type of infection and how long did it last?

_____

Have you been hospitalized within the past 3 months? If yes, why?

_____

Have you been diagnosed with any chronic illness such as cancer, chronic fatigue syndrome, acute or chronic active hepatitis, Type 1 diabetes mellitus or autoimmune disease? If yes, please list.

_____

Have you ever had any of the following symptoms? (These are exclusionary.)

	Last date it occurred	Duration of last occurrence	Total # of episodes
History of dizzy spells?	_____	_____	_____
Angina pectoris?	_____	_____	_____
Irregular heart beats?	_____	_____	_____
Heart attacks?	_____	_____	_____
Stroke?	_____	_____	_____
Seizure disorder?	_____	_____	_____
Diabetes?	_____	_____	_____
Asthma?	_____	_____	_____
Seasonal Allergies?	_____	_____	_____
Dyspnea?	_____	_____	_____

Have you ever used recreational drugs like marijuana, cocaine, crystal methamphetamines, crack, etc.? If yes, which one(s) did you use, how often?

_____

When was the last time you used recreational drugs?
List amount, last time used and type used.

_____

Are you currently using recreational drugs? If yes, list amount and type.

_____

Now I am going to ask you questions about current/previous exercise program (ACSM guidelines used for minimum frequency, intensity, duration).

Do you currently participate in any type of exercise program? _____

If yes, which, if any, types of exercise did you participate?

Type of Exercise	Yes/No	Frequency	Duration	Intensity
Walk on treadmill	_____	_____	_____	_____
Run on treadmill	_____	_____	_____	_____
Walk/run on treadmill	_____	_____	_____	_____
Stationary bicycle	_____	_____	_____	_____
Spinning class	_____	_____	_____	_____
Outdoor bicycle	_____	_____	_____	_____
Step aerobics	_____	_____	_____	_____
Floor aerobics	_____	_____	_____	_____
Boxing class	_____	_____	_____	_____
Kickboxing class	_____	_____	_____	_____
Body conditioning class (combination of step/floor aerobics and light weights)	_____	_____	_____	_____
Pilates	_____	_____	_____	_____
Yoga	_____	_____	_____	_____
Weight training (heavy)	_____	_____	_____	_____

How long have you been doing your current exercise program? _____

If you do not currently participate in an exercise program, how long ago did you participate in a regular exercise program and what type of exercise(s) did you regularly do?

_____

Have you ever done an exercise test to determine your fitness level? _____
(Explain the test to the prospective subject.)

Have you ever done a spirometry test to determine how well your lungs work? _____
(Explain the test to the prospective subject.)

Are you willing to come to the Exercise Lab and do a spirometry and exercise test? ____

What is your availability to come to the Lab over the next month? (Explain that the informed consent process, test prep, testing and clean-up will take approximately 2 hours.)

Do you have any questions? Thank you for your time.

If you are eligible for the study, I will contact you to set-up a convenient time for you to come to the Exercise Lab to do the required testing.

APPENDIX B: INFORMED CONSENT FORM

Subject Informed Consent Form

HIV-1 Seropositive Lung Function Study

PURPOSE: The purpose of this study is to determine if there are any differences in lung function at rest and during dynamic exercise between sedentary, resistance-trained and aerobically trained early symptomatic HIV-1 seropositive men.

PROCEDURES: This study will take approximately2 hours. Procedures will be performed at the Center for Exercise Medicine located on the 14th floor of the Jackson Medical Towers directly across from the Miami Veterans Administration Medical Center.

CONFIDENTIALITY: Your consent to participate in this study includes consenting to allowing the Investigator and his/her assistants review all your medical records as determined necessary for the purposes of this study. The Investigator and his/her assistants will consider your records extremely confidential to the extent permitted by law. The results of the study, including laboratory tests, may be published for scientific purposes and your signature on this form means that you agree to this. Your records and results will not be identified as pertinent to you specifically in any publication without your expressed written permission.

In rare circumstances, the U.S, Food and Drug Administration (FDA) or the U.S. Department of Health and Human Services (DHSS) may request copies of your records. If this happens, the FDA or DHSS requests will be honored.

RIGHT TO WITHDRAW: Participation in this study is voluntary. You are free to withdraw your consent and discontinue your participation at any time. Your current or future medical care will not be prejudiced by withdrawal from the study orr by lack of participation.

You should also understand that the physician in charge can remove you from the study without your consent either because he/she feels it is in your best interest or from failure to follow the study procedures.

QUESTIONS: You are encouraged to ask any and all questions which come to your mind concerning this study. The staff of the research program will be happy to discuss any questions with you. At the completion of the study, the staff will discuss with you whatever results are available and provide these results to you.

If requested, you will be provided with a copy of your signed informed consent form. In the event of a research-related injury, you should contact the Principal Investigator immediately.

If you have any questions, about your rights as a research subject, you may contact Maria Arnold at 305-547-3327.

I understand what is expected of me and I consent to participate in this study.

_____
NAME OF SUBJECT (Print)

_____ _____
SIGNATURE OF SUBJECT DATE

_____ _____
SIGNATURE OF WITNESS DATE

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