Cardiovascular disease risk and central and peripheral responses to exercise in individuals with spinal cord injury

by

Dominik Zbogar

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Abstract

Introduction: Persons with spinal cord injury (SCI) are often physically inactive and as such are at increased risk of cardiovascular morbidity. Fortunately, exercise training in SCI can provide improve health-related physical fitness and alleviate medical complications associated with deconditioning. To optimize health-related fitness gains of exercise in SCI and maximize the potential for chronic disease prevention it is necessary to understand the acute responses (central and peripheral) to exercise.

Purposes: The primary purposes of this research were to: 1) determine the contribution of central/peripheral limitations to exercise capacity and 2) examine vascular health in SCI.

Methods: Seven persons with paraplegia and seven able-bodied (AB) individuals participated in two testing days. Testing day one consisted of incremental arm crank ergometry to exhaustion with measures of cardiac output, muscle oxygenation, and expired gas and ventilatory parameters. Testing day two involved the measurement of arterial compliance and endothelial function.

Results: There was a significant difference for small artery compliance between SCI and AB (6.9±3.7 versus 10.5±1.7ml mmHg⁻¹x100, p< 0.05). Arm total haemoglobin increased significantly throughout exercise. Arm oxygenation decreased until 60% of maximal wattage after which values did not change. Though non-significant, the large effect size (eta²=.142) suggests a trend for higher aerobic power in AB (28.6±5.7mL·kg⁻¹·min⁻¹) than in SCI (23.7±2.77mL·kg⁻¹·min⁻¹) due to a trend for higher cardiac output values in AB (18.0±5.7L·min⁻¹) than SCI (15.8±3.4L·min⁻¹) at maximal exercise.

Conclusions: Small artery compliance is lower in SCI than AB. Leveling off of deoxygenated haemoglobin with total haemoglobin increasing throughout exercise suggests a peripheral limitation to arm ergometry in both groups. A trend for higher cardiac output in AB suggests a central limitation in SCI.
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1. **Introduction**

   In Canada annual incidence rates of spinal cord injury (SCI) are estimated to be 35 per year per million population (CPA 2009). In terms of prevalence, approximately 36,000 Canadians live with spinal cord injury (SCI) (BCPA 2006), 80% of which are experienced by individuals under age 30 (ICORD 2009). Advances in medical treatment over the past several decades have increased significantly the life expectancy of these individuals (Hicks et al. 2003; Strauss et al. 2006; Warburton et al. 2006b). As many individuals with SCI now live a longer lifespan (Glaser 1985; ICORD 2009), they are at risk for developing the same chronic conditions (such as heart disease and cancer) as able-bodied persons (DeVivo et al. 1999). Over the past several decades cardiovascular disease has become the leading cause of death in the SCI population (Le and Price 1982; Bauman et al. 1992; Bauman et al. 1999a; Myers et al. 2007). The increase in cardiovascular disease (Whiteneck et al. 1992; Bauman et al. 1999a; Bauman et al. 1999b; Jacobs and Nash 2004) as well as asymptomatic cardiovascular disease (Bauman et al. 1992; Bauman et al. 1993; Bauman et al. 1994; Jacobs and Nash 2004) with aging in SCI individuals reflects that of able bodied individuals, though at an accelerated rate, higher prevalence, and earlier onset.

   Given the increased life expectancy of individuals with SCI, considerable SCI research has focused on the management of health issues associated with long-term survival (Ginis et al. 2005). A physically inactive lifestyle is associated with premature mortality and increased risk for chronic disease (including heart disease) (LaMonte and Blair 2006; Warburton et al. 2006a; Warburton et al. 2006b). This is a significant risk for persons with SCI who, because of loss of motor function, are often extremely sedentary (Laporte et al. 1984; Jacobs and Nash 2004). As a result, they have low levels of cardiovascular fitness (Hoffman 1986b), and are at increased risk of cardiovascular-related morbidity and mortality (Jacobs and Nash 2004). Normal wheelchair activities, i.e. most
activities of daily living, are often not adequate to maintain cardiovascular fitness in persons with
SCI (Hoffman 1986b; Figoni 1990; Janssen et al. 1994; Vidal et al. 2003). For instance,
approximately one quarter of paraplegics do not achieve aerobic power (VO2) levels on arm
ergometry tests sufficient to perform many activities of daily living (Noreau et al. 1993). Decreased
cardiovascular fitness may result in a cycle of further physical decline, ultimately reducing the
individual’s functional capacity and the ability to live independently, and increasing cardiovascular
disease risk (Warburton et al. 2006b).

In addition to fitness gains, appropriate exercise training in individuals with SCI has the
potential to alleviate medical complications associated with being very physically inactive (e.g.
cardiovascular disease, decubitus ulcers, orthostatic hypotension) and improve rehabilitation
outcome (Glaser 1989). However, while there are various exercise programs prescribed to
individuals with SCI, most are based on studies of able bodied individuals (Hoffman 1986a).
Consequently, the development of optimal rehabilitation exercise programs for individuals with SCI
has yet to occur (Warburton et al. 2006b). In order to optimize the aerobic fitness gains and health
outcomes of exercise in SCI and to maximize the potential for chronic disease prevention, it is
necessary to understand the acute exercise response (e.g., central and peripheral limitations) of
these individuals.

Individuals with SCI exhibit an increased incidence of hyperlipidaemia, hypertension, type
II diabetes, and hyperinsulinaemia (Bauman et al. 1992; Bauman et al. 1999a) and diminished
aerobic fitness which are all cardiovascular disease risk factors (Hoffman 1986b; Wecht et al.
2000; Wecht et al. 2003). The endothelium is a layer of cells that lines every blood vessel in the
body. Due to its location and its numerous functions, endothelial dysfunction and the
accompanying structural and functional changes in the arterial wall are one of the earliest events in
the pathogenesis of cardiovascular disease and is widely regarded as a necessary first step in the
development of atherosclerosis (Ross 1993; Behrendt and Ganz 2002). When damage occurs to
the endothelium via any of the above-mentioned cardiovascular disease risk factors, its protective
properties are compromised which leads to intimal hyperplasia and a chronic inflammatory state
that creates an atherosclerotic lesion (Rubanyi 1993). Inasmuch as this reduced function
influences the tone of the arterioles, the increasing blood pressure and decreasing arterial
compliance may be manifestations of the atherosclerotic process (Ross 1993; Cohn et al. 2004). It
is therefore important to investigate the vascular health of individuals with SCI and the utility of
early markers of vascular disease such as measuring arterial compliance and endothelial function.

2. Purposes

This study examined the cardiac, vascular and peripheral muscle function of persons with
SCI in comparison to the general population. The primary purpose of this investigation was to
determine the contribution of central (cardiac output) and peripheral (ability to extract and utilize
oxygen) limitations to exercise capacity in individuals with spinal cord injury. The secondary
purpose of this study was to determine the vascular health of individuals with SCI relative to able-bodied individuals. The tertiary purpose of this study was to examine quality of life (QOL) in persons with SCI compared to able bodied controls. Given the smaller number of participants and exploratory nature of this study we have included information on effect size to assist other investigators to determine appropriate participant numbers for parameters being measured in future studies.
3. **Objectives**

3.1. **Cardiovascular parameters**

To investigate differences in central limitations we investigated differences the response of stroke volume (SV) and cardiac output (Q) between individuals with SCI and able-bodied controls. To investigate differences peripheral limitations we investigated responses in muscle oxygenation and arteriovenous oxygen difference (avDO₂) during the arm crank ergometry protocol between individuals with SCI and able-bodied controls.

3.2. **Vascular Health**

Following that individuals with SCI are increased risk of cardiovascular disease we wished to investigate the utility of two measures which serve as early markers of cardiovascular disease. Thus it was our objective to investigate differences in both endothelial function and arterial compliance between individuals with SCI and able bodied controls.

3.3. **Quality of life**

Questionnaires measuring QOL can be categorized as either subjective or objective measures. Few studies investigating cardiovascular function in SCI have included measures of QOL (Hicks et al. 2003). Although individuals with SCI are living longer (Glaser 1985; DeVivo et al. 1999), their QOL may remain low. Therefore it was our objective to investigate differences in subjective and objective measures of QOL between groups.
4. **Hypotheses**

4.1. **Cardiovascular parameters**

We hypothesized that individuals with SCI will exhibit a lower SV and Q compared to able bodied controls which would be indicative of central limitation. With respect to peripheral limitation we anticipated that muscle oxygenation during the arm crank ergometry protocol would decrease to a greater extent in individuals with SCI.

4.2. **Vascular Health**

We hypothesized that endothelial function would be reduced in SCI individuals compared to able bodied individuals. Additionally we hypothesized that arterial compliance, specifically small artery compliance, would be lower in SCI compared to able bodied individuals.

4.3. **Quality of life**

We anticipated that able-bodied individuals would have a higher QOL, as measured by subjective and objective questionnaires, than individuals with SCI.

5. **Central and Peripheral Adaptations and Limitations to Exercise**

5.1. **Background**

The transport of oxygen in the body is composed of the interaction of central and peripheral steps summarized by the Fick principle:

\[ VO_2 = HR \times SV \times avDO_2 \]

where \( VO_2 \) is aerobic power, \( HR \) is heart rate, \( SV \) is stroke volume, and \( avDO_2 \) is arteriovenous oxygen difference. Stroke volume is determined by several factors. End diastolic volume influences
stroke volume as strength of ventricular contraction is increased by an enlargement of end diastolic volume via the Frank-Starling law of the heart; the increase in end diastolic volume results in a lengthening of cardiac muscle fibres which improves the force of contraction (Levine 2008). Increased cardiac contractility increases SV through increased force generation independent of end diastolic volume. The result of increased force generation is a reduction in end systolic volume and higher SV. Total peripheral resistance affects SV in that arteriolar dilatation with exercise decreases total peripheral resistance making it easier for the heart to pump blood through enlarged SV (Warburton et al. 2002). The amount that these variables can increase with exercise defines VO_{2}\text{max} (Wagner 1991). Traditionally, the cause of the limit to oxygen consumption has been sought in the respiratory system and the heart and its capacity to pump blood (central factors), and in the peripheral circulation and the metabolic capacity of active muscles (peripheral factors) (Gonzalez-Alonso and Calbet 2003). Respiratory limitations are not common in normally active people exercising at sea level as the respiratory system is more than capable of moving oxygen from the air to the gas-blood interface even during the most severe metabolic demands (Dempsey et al. 1990). It is true that the respiratory system is a limitation in pulmonary gas exchange in patients with pulmonary disease (Dempsey et al. 1990). Respiratory limitation can also occur in endurance athletes with very high maximal Q. In this situation, hypoxemia, caused by diffusion limitation which is related to high pulmonary blood flow and short pulmonary mean transit time limits time for oxygen transfer from alveoli to red blood cells (Dempsey et al. 2008). The consequence, expressed in terms of the Fick Principle, is a decrease in arterial oxygen content which reduces VO_{2}\text{max} in proportion to the narrowing of avDO_{2}. Individuals with paraplegia have full innervation to both primary and a number of accessory muscles of inspiration since injury is below the cervical level (Sheel et al. 2008) and consequently their respiratory function is comparable to that in the able bodied population (Haisma et al. 2006). In addition the maximal Q
elicited by arm ergometry is significantly lower than that attainable by leg ergometry (Sawka 1986; Myers et al. 2007). Therefore it is unlikely that respiratory limitations would become a factor in this investigation.

The main arguments for Q as a limit to VO$_{2\max}$ are: 1) VO$_{2\max}$ is achieved when an individual intensely activates approximately ½ of total muscle mass. The addition of more active muscle at VO$_{2\max}$ causes no further increase in Q or oxygen uptake; the heart cannot provide enough blood flow for all the muscles. 2) The addition of muscles at VO$_{2\max}$ results in vasoconstriction in the active muscle to maintain arterial pressure (Gonzalez-Alonso and Calbet 2003). 3) The capacity of muscles to consume oxygen exceeds that which the heart can deliver (Richardson et al. 1999). Another potential central limitation lies with the pericardium that surrounds the heart as, since it limits myocardial distention, it can constrain diastolic filling (Esch et al. 2007). Pericardectomy in foxhounds removed a mechanical constraint on SV and enabled the heart to respond to the high filling pressure at maximal exercise. This resulted in a significantly higher SV, Q and VO$_{2\max}$ (Stray-Gundersen et al. 1986). This decrease in mechanical constraint allows for an increased left ventricular end diastolic volume and consequently increased SV. Pericardectomy in pigs has yielded the same results (Hammond et al. 1992). It appears that chronic aerobic exercise can induce pericardial remodelling since endurance trained athletes exhibit end diastolic pressure-volume curves similar to those observed in animal hearts following pericardectomy (Esch et al. 2007). The observation that endurance-trained athletes have an enhanced filling capacity and ability to increase SV to a greater degree than untrained persons (Gledhill et al. 1994; Warburton et al. 2002) supports the contention that endurance-trained athletes possess an altered pericardium.

The $avDO_2$ component of the Fick equation can be divided into CaO$_2$ and CvO$_2$, the arterial and venous content of oxygen, respectively. An increase in $avDO_2$ can be the result of elevated
CaO₂ or a decrease in CvO₂. Haemoglobin concentration does not change with training and the arterial pressure of oxygen is usually sufficient to maintain arterial saturation of haemoglobin which means that ordinarily CaO₂ does not change (Rowell 1986). However, research which increases CaO₂ by increasing inspired oxygen tension (Hopman et al. 2004) or by raising haemoglobin concentration (Spriet et al. 1986) raises VO₂max, which indicates that muscle metabolism is not limiting.

The decrease in CvO₂ with exercise is a result of increased oxygen extraction by active muscles. With training this ability of active muscle to extract oxygen is increased. Adjustments within the muscle that may explain the greater extraction is a decrease in the distance for diffusion of O₂ between capillaries and cells which is afforded by increased capillarization (Daussin et al. 2007). There is evidence to show that a diffusion limitation between the capillaries and the mitochondria could occur in normoxia (Roca et al. 1989). However, peak VO₂ is increased if this diffusion limitation is overcome with more oxygen made available to the mitochondria (Richardson et al. 1999; Saltin and Calbet 2006).

A reduction in HR at rest and during standard submaximal workloads, with an inherent reduction in myocardial aerobic requirements, is a significant adaptation to chronic aerobic exercise of a sufficient intensity in able-bodied persons. This response reflects both central and peripheral adaptations (Clausen et al. 1970; Rowell 1986; Daussin et al. 2007). Central adaptations involve improved ability of the heart to deliver blood to working tissues manifested as an enhanced Q with a compensatory decrease in sympathetic stimulation (Frick et al. 1967; Clausen 1977; Mclean and Skinner 1995). The higher blood volume that results from chronic endurance training is a major contributor to enhanced ventricular function (Hopper et al. 1988). These higher blood volumes result in an increased end diastolic volume which increases SV through the Frank-Starling mechanism (Rowell 1986; Phillips et al. 1998; Warburton et al. 2002). In addition, since trained
individuals have lower blood pressure, ventricular emptying is facilitated by a decrease in afterload, also increasing SV (Gledhill et al. 1994). An improvement in ventricular filling time is responsible for the finding that in trained athletes SV does not plateau as it does in sedentary counterparts (Gledhill et al. 1994; Warburton et al. 2002).

Decreased afterload is attributed to a decrease in sympathetic nervous system activity in the working muscle which is also responsible for the increased blood flow, a peripheral adaptation. Other peripheral adaptations, as mentioned, involve increased metabolic capacity in skeletal muscles resulting from increased capillarization and mitochondrial density. These peripheral changes manifest as an increase in avDO₂ (Clausen 1977; Rowell 1986; Mclean and Skinner 1995; Daussin et al. 2007).

Central improvements after training will result from increased volume loading by maximally stressing the capacity of the heart and circulation to deliver blood and oxygen to the working muscles. Central circulatory adaptations are more likely to occur when training uses large muscle groups to create high levels of oxygen uptake and Q, as seen in running and cycling (Clausen 1977; Reading et al. 1993; Daussin et al. 2007). Peripheral adaptations in skeletal muscle that occur after training large muscle groups can also be obtained through exercise using smaller muscle groups such as during arm ergometry, although central adaptations are minimized (Clausen 1977). It is believed that central adaptations to training are more beneficial than peripheral adaptations in decreasing cardiovascular disease risk (Mclean and Skinner 1995).

5.2. Physiology of arm exercise

At any given submaximal power output, HR, systolic and diastolic pressure, minute ventilation, and oxygen uptake are higher during arm exercise compared to leg exercise, while SV
is lower in arm exercise than in leg exercise (Stenberg et al. 1967; Franklin 1985; Jacobs and Nash 2004). Cardiac output remains the same, though it is achieved by differences in HR and SV contributions (Sawka 1986). Several factors may account for the difference in cardiorespiratory responses to the two modes of exercise at equal workloads. Diastolic filling rate and end diastolic volume is lower in arm exercise than in leg exercise which results in a lower SV (Goodman et al. 2007). Mechanical efficiency (work/VO₂) is lower during arm exercise (Stenberg et al. 1967; Phillips et al. 1998). This may result from the use of smaller muscle mass and the static effort of the torso muscles and hands required of arm work, which increases VO₂ without increasing work output (Franklin 1985; Phillips et al. 1998). The higher rate pressure product (a product of HR and systolic blood pressure) at a given workload for arm exercise compared to leg exercise is thought to reflect increased sympathetic tone during arm exercise, potentially mediated by any combination of: reduced SV with consequent tachycardia, isometric contraction of torso muscles, and sympathetic vasoconstriction in the non-working leg musculature (Franklin 1985; Phillips et al. 1998) which elicits a greater total peripheral resistance and arterial blood pressure during arm exercise, which can increase afterload, limit left ventricular ejection and decrease SV (Goodman et al. 2007).

With maximal exercise, VO₂max is lower during arm ergometry, averaging 70% compared to cycling (Sawka 1986; Phillips et al. 1998; Secher and Volianitis 2006). A lower VO₂max is attributed to a smaller skeletal muscle mass which results in a decreased oxidative capacity and a reduced ability to create tension (Sawka 1986; Phillips et al. 1998). Maximal Q is also significantly lower (approximately 30%) for arm exercise which corresponds to the lower VO₂max (Sawka 1986; Myers et al. 2007).
5.3. **Acute limitations in SCI**

For individuals with SCI who are confined to arm exercise, the ability to generate higher levels of VO₂ is further reduced due to metabolic, hormonal, and hemodynamic disturbances related to their injury. Consequently, voluntary exercise capacity in individuals with SCI is lower (Jacobs and Nash 2004) as is the level of aerobic fitness that may be achieved through training (Glaser 1989).

Although individuals with paraplegia may show pronounced hypertrophy of the arms due to their use in ambulation, they are not able to make use of trunk and leg muscles for stabilization and as a fulcrum with which to push during arm exercise (Hopman et al. 2004). They are not able to recruit their muscles as effectively and consequently they attain lower VO₂peak values than able bodied individuals (Hopman et al. 2004).

There is also a significant elevation of resting and exercising HR in partial compensation for a decreased SV in individuals with SCI to maintain Q (Jacobs and Nash 2004). Decreased SV is due to a decreased venous return, resulting in reduced filling pressure and end-diastolic volumes (Jacobs and Nash 2004) caused by impaired blood redistribution during exercise resulting from absence of the muscle pump in paralyzed legs and centrally mediated sympathetic control (Hopman et al. 1992; Hopman et al. 2004).

Additionally, aerobic capacity in SCI individuals can be limited by diminished sympathetic outflow since the normal cardiovascular response involves intact sympathetic reflexes. Normal sympathetic reflexes increase blood flow to metabolically active skeletal muscles to increase oxygen and fuel substrate provision and metabolite removal (Glaser 1985; Myers et al. 2007). This process involves vasoconstriction of relatively inactive tissues (e.g. viscera, skin, and non-exercising muscle), vasoconstriction, vasodilation of arterioles in exercising muscle, increased HR and contractility and Q. The loss of active muscle and sympathetic contributions in exercise can
result in high fatigability of exercising muscle due to smaller mass, inadequate blood flow, more anaerobic contribution and increased accumulation of metabolites in muscles (Glaser 1989).

Thus, the stimulus of arm exercise may not be sufficient to increase SV appreciably (Clausen 1977). Spinal cord injury disturbs venous return (Jacobs and Nash 2004) and sympathetic reflexes (Glaser 1989). These factors can lead to reduced stress in the form of volume loading placed on the heart during exercise, therefore reducing potential for central adaptations. The ability to stress central haemodynamic mechanisms is further compromised when exercising in the traditional upright seated position (Phillips et al. 1998). All these factors, in accordance with the Frank-Starling mechanism, combine to produce a lower SV compared with able-bodied persons under similar exercise conditions (Phillips et al. 1998), limiting the potential to improve cardiovascular fitness.

However, research has yielded conflicting results. In a study by Hopman et al. (1998) investigating maximal exercise in SCI, there was no change in VO_2peak despite various interventions to increase SV. These findings suggest that a peripheral limitation (oxygen utilization) is the limiting factor in VO_2peak during arm exercise in SCI individuals. Another study by the same group (Hopman et al. 2004) showed differing results with VO_2 during peak exercise increasing with hyperoxia in paraplegics indicating that VO_2peak during arm exercise is limited by oxygen supply rather than by small muscle mass and related biochemical limitations. Another study shows that in paraplegics, central mechanisms can be stressed during arm ergometry since after a training stimulus there was a significant increase of 31% in VO_2 related to a SV increase of 16% (Davis et al. 1987). The apparently conflicting results of different studies may be explained by the different stimuli they apply to investigate central versus peripheral limitations to exercise. It is possible that there is no one single limitation to VO_2max but that there are several areas of limitation and therefore several areas in which aerobic power can be manipulated.
5.4. Chronic exercise responses in SCI

Numerous reviews have reported that exercise rehabilitation is an effective means of reducing disease susceptibility in persons with SCI (Glaser 1985; Hoffman 1986a; Glaser 1989; Figoni 1990; Jacobs and Nash 2004; Warburton et al. 2006b). Research has shown that endurance, arm strength, peak power output and VO$_2$peak can improve through arm training (Figoni 1990). However, the nature of the cardiovascular training response to arm exercise is not well understood (Figoni 1990) and studies investigating the potential for central adaptations have been controversial (Hoffman 1986a). Thus it is unclear whether changes in VO$_2$peak result from central (HR, SV, Q) adaptations or increases in peripheral oxygen extraction (avDO$_2$) or which changes are more important (ACSM 2002; Jacobs and Nash 2004). Due to the relatively small muscle mass involved in activities such as wheelchair propulsion or arm ergometry, there is potentially a decreased ability to perform aerobic exercise that will create sufficient stimulus for myocardial adaptations (Figoni 1990); thus training is often expected to result in peripheral adaptations (Hoffman 1986a). For example, a study investigating the effect of functional electrical stimulation leg cycle ergometry (FES-LCE) which may promote greater central haemodynamic responses than arm ergometry concluded that because of a lack of increase in post-training VO$_2$ or Q with the untrained upper extremities that peripheral adaptations were responsible for training changes (Hooker et al. 1992). However, most studies have not directly measured Q during exercise in those with SCI (Warburton et al. 2006b), a consequence of the difficulty inherent in measuring Q during maximal exercise (Warburton et al. 1999).
5.5. Measurement of Central and Peripheral Responses

5.5.1. Central limitations: Acetylene Rebreathing

The measurement of Q is an important tool in quantifying the central limitations and adaptations to exercise. There are numerous methods of measuring Q, both invasive and non-invasive (Warburton et al. 1999). The use of foreign gas techniques, specifically acetylene rebreathing to measure Q has been in use since the 1920s (Grollman 1929). Acetylene rebreathing has become one of the most commonly used non-invasive methods of measuring cardiac output, as it is highly reproducible (Warburton et al. 1998). The accuracy of acetylene rebreathing rivals "gold standard" invasive procedures of measuring Q and it has been validated at rest and during submaximal and maximal exercise (Warburton et al. 1999).

Rebreathing techniques involve the inhalation of a mixture of soluble (acetylene) and insoluble (helium) inert gases (Cabrera et al. 1991). The transport of a gas in blood is determined by its diffusivity and solubility (Warburton et al. 1998). Because acetylene is soluble and does not bind with haemoglobin, it rapidly diffuses across the lung blood-gas barrier and its removal from the lungs is determined by blood flow through the pulmonary capillaries (Warburton et al. 1998; Warburton et al. 1999). Pulmonary blood flow is taken as Q. Helium, the insoluble gas, is used to determine the gas volume in the system (Cabrera et al. 1991) and to confirm that adequate mixing of the rebreathing system has occurred (Warburton et al. 1999). It is important, in the SCI population, to obtain direct measures of Q and aerobic power as submaximal prediction can be complicated by impairment of sympathetic innervation to the heart (Warburton et al. 2006b).

5.5.2. Peripheral limitations: Near Infrared Spectroscopy and Arteriovenous Oxygen Difference

Near infrared spectroscopy (NIRS) is a validated non-invasive technique that measures relative changes in skeletal muscle oxygenation during exercise (Mancini et al. 1994; Bhambhani
Near infrared light readily penetrates biological tissue and, with the use of the modified Beer-Lambert Law which states that change in light attenuation is proportional to the changes in the concentrations of tissue chromophores (Kocsis et al. 2006), NIRS allows for detection of changes in specific chromophores in humans (Boushel et al. 2001).

Three molecules are known to affect near infrared light absorption during changes in oxygen tension, haemoglobin, myoglobin, and cytochrome c oxidase (Boushel and Piantadosi 2000). In skeletal muscle, the NIRS signal is mainly derived from the absorption of light by haemoglobin in small arterioles, capillaries, and venules (Boushel et al. 2001). Since the absorption spectra of myoglobin and haemoglobin overlap, NIRS does not differentiate between these signals in vivo (Boushel et al. 2001). However, myoglobin occupies approximately 10% of the NIRS light absorption signal (Mancini et al. 1994; Boushel et al. 2001) and cytochrome c oxidase contributes approximately 2-3% (Boushel et al. 2001), thus the NIRS signal is primarily derived from haemoglobin. At 760nM deoxygenated haemoglobin has a higher light absorbency and oxygenated haemoglobin has a higher absorbency at 850nM (Mancini et al. 1994; McCully and Hamaoka 2000). Monitoring concentration changes in these two wavelengths provides an index of relative tissue deoxygenation.

For every pulse of near infrared light emitted into the tissue there are billions of photons. On average, for every 100 million photons emitted, one will arrive at the detection probe. The remainder are either absorbed or scattered (Gagnon et al. 2001). The most widely used and versatile NIRS devices are continuous wave spectrometers (Boushel et al. 2001) which use reflected light to study skeletal muscle (McCully and Hamaoka 2000). However, because the pathlength of the light from emitter to detector is unknown (McCully and Hamaoka 2000) and because there is no distinction between absorbed or scattered light, quantifying the absolute concentration of any chromophores in the tissue being illuminated remains challenging (Gagnon et al. 2001).
Instead, continuous NIRS provides trends in the responses of the chromophores to changes in oxygen availability and utilization from a baseline value (Boushel and Piantadosi 2000; Boushel et al. 2001). Using NIRS to measure blood flow requires the use of a light-absorbing tracer (Boushel and Piantadosi 2000). Thus, while total haemoglobin is referred to as a surrogate for blood flow in this study, without the use of a tracer, changes in this variable can be caused by increased blood flow, venous obstruction or increased haemoglobin concentration. Increased oxygenated haemoglobin can indicate increased arterial inflow, increased oxygen saturation or an increased concentration of oxygenated haemoglobin (Raisis 2005). Despite these limitations, NIRS does provide important information regarding trends in muscle oxygenation during exercise and recovery and is a valuable tool in helping to understand the physiology of exercise (Bhambhani et al. 1998).

During exercise in humans, NIRS has been extensively used to measure blood flow in the quadriceps of able-bodied individuals (Bhambhani et al. 1998; Kawaguchi et al. 2008; Kennedy et al. 2006) and during leg exercise in clinical populations such as persons with heart failure (Wilson et al. 1989). However, NIRS has been used to a lesser degree during arm ergometry (Jensenurstad et al. 1995). Near infrared spectroscopy has also been used to investigate muscle oxygenation in the paralyzed legs of individuals with SCI during FES cycling (Bhambhani et al. 2000) and passive leg movement (Kawashima et al. 2005). However, the measurement of NIRS in arm ergometry in the SCI population has not been investigated.

Discussion of avDO₂ and its potential role as a limitation during exercise is addressed in section 5.1. The avDO₂ depends mainly on the exchange area between the capillary blood and the muscle cells, as well as on the skeletal muscle maximal oxidative capacity (Daussin et al. 2007). Thus it provides information on the peripheral muscle response to exercise. Since we are measuring VO₂ and Q in this study, this peripheral factor will be obtained by manipulation of the Fick equation to solve for avDO₂: \( avDO₂ = \frac{VO₂}{Q} \).
6. **Endothelial Function**

6.1. **Background**

The vascular endothelium is a monolayer of interlinked cells that compose the innermost layer of blood vessels (Volker 2005). The endothelium works to maintain vascular health through a variety of mechanisms (Ross 1993), sensing changes in its environment and responding to these stimuli through the production of various biologically active substances that modulate the tone and structure of the underlying smooth muscle (Rubanyi 1993; Maiorana et al. 2003). The endothelium serves several vital functions. Endothelial cells tightly interlock to form a selective barrier such that passage from the blood into the tissue occurs through the endothelial cell (Ross 1993; Rubanyi 1993). The endothelium is involved in capillary transport of water and solutes. It produces and releases factors that promote or inhibit growth of smooth muscle. A number of antithrombotic, anticoagulant, and fibrinolytic factors are released by the endothelium, providing a non-adhesive luminal wall (Ross 1993; Behrendt and Ganz 2002; Cohn et al. 2004). The endothelium participates in inflammatory and immune responses, regulates plasma lipids and is involved in angiogenesis and tumour metastasis (Rubanyi 1993). The endothelium is integral to the maintenance of cardiovascular homeostasis, producing and secreting vasoactive substances that manipulate vascular tone, and adjusting to the variable haemodynamic and hormonal environment (Rubanyi 1993).

It is the regulation of vascular tone that has been the most comprehensively studied aspect of the endothelium (Maiorana et al. 2003). Regulation of vascular tone is accomplished by endothelium-derived vasoactive relaxing and contracting factors (Rubanyi 1993). Relaxing factors include prostacyclin, endothelium-derived hyperpolarizing factor and nitric oxide (NO) (Rubanyi 1993). Nitric oxide is generated by the conversion of the amino acid L-arginine to NO and L-
citrulline by the enzyme nitric oxide synthase III which is constitutively active in the endothelium (Palmer et al. 1988; Volker 2005). Nitric oxide elevates cyclic guanosine monophosphate in vascular smooth muscle which causes it to relax. While numerous factors with complex interactions contribute to the extent of vasomotor control, NO is considered the most important relaxing factor (Moyna and Thompson 2004; Walther et al. 2004). Relaxing factors can be released via numerous stimuli including platelet products, thrombin, hormones, neurotransmitters, changes in oxygen tension, and shear stress (Vanhoutte et al. 1986). Constricting factors include endothelin-1, platelet-activating factor, and angiotensin II (Volker 2005). Constricting factors can be released by acetylcholine, arachidonic acid, norepinephrine, prostaglandin H₂, thrombin, from pharmacological agents such as nicotine and high potassium, hypoxia, and pressure and stretch (Volker 2005).

6.2. Measuring Endothelial Function

Endothelial dysfunction is manifested in impaired endothelium-dependent vasodilatation caused by reduced synthesis/release of NO (Rubanyi 1993). One should note that NO-related vasodilatation is but one of the endothelium related effects of NO and that NO is one of many mediators produced by the endothelium (Maiorana et al. 2003). Nevertheless, testing of endothelium-dependent vasodilatation is a useful tool for assessing the functional integrity of vascular endothelium in vivo, serving as a surrogate for the bioavailability of NO (Behrendt and Ganz 2002).

Inhibitors of nitric oxide synthase III, such as N⁶-monomethyl-L-arginine (L-NMMA) are infused to examine ambient NO bioactivity in resting muscle (Green et al. 2004). Endothelium-dependent vasodilators, such as acetylcholine, are used to stimulate NO release from endothelial cells (Maiorana et al. 2003). It is thought that acetylcholine exerts its vasodilatory effect by binding to the muscarine receptor to activate nitric oxide synthase III (Higashi and Yoshizumi 2003).
Similarly, endothelium-independent NO vasodilator function is assessed by infusing sodium nitroprusside or administering sublingual nitroglycerin which donates NO directly to vascular smooth muscle (Cohn et al. 2004; Green et al. 2004).

6.2.1. Doppler Ultrasonography

The infusion of acetylcholine, while the gold standard in the measurement of endothelial function, is invasive. Using high resolution Doppler ultrasonography to measure post-ischaemic flow-mediated dilatation (FMD) of the brachial artery is one of the most frequently used and well validated non-invasive techniques to assess endothelial function in peripheral arteries (Deanfield et al. 2005). Flow-mediated dilatation is depressed in those with atherosclerosis and cardiovascular disease risk factors (Celermajer et al. 1992; Joannides et al. 1995) and correlates well with coronary vascular endothelial function (Anderson et al. 1995).

It is believed that the vasodilatation of reactive hyperaemia that follows a period of limb ischaemia comes as a result of increased NO, stimulated by changes in shear stress detected by endothelial cells (Kuo et al. 1990; Fathi and Marwick 2001; Green et al. 2004). This process is not fully understood, but likely involves calcium activated potassium-channel opening, membrane hyperpolarization, and calcium-mediated activation of nitric oxide synthase III (Deanfield et al. 2005).

Depending on the site of occlusion, vasodilatation during reactive hyperaemia is not solely a result of NO (Doshi et al. 2001) as inhibition of NO using L-NMMA does not completely inhibit the forearm vascular relaxation caused by reactive hyperaemia induced by upper arm occlusion (Doshi et al. 2001). However, NO does play a major role in limb blood flow response to reactive hyperaemia (Higashi and Yoshizumi 2003) specifically when occlusion is performed distal to the elbow (Doshi et al. 2001). Various other factors affect the measurement of flow mediated vascular
reactivity such as food, drugs, exercise and temperature (Corretti et al. 2002). These factors should all be addressed or controlled before measurement begins.

6.3. Pathophysiology of the endothelium

The endothelium plays an important role in cardiovascular health and disease owing to its location and numerous functions (Rubanyi 1993; Behrendt and Ganz 2002). Endothelial dysfunction has been documented in manifest cardiovascular disease and coronary atherosclerosis (Sorensen et al. 1997; Walther et al. 2004). It has also been found in the presence of various coronary risk factors (Celermajer et al. 1994) such as hypertension (Panza et al. 1990), hypercholesterolemia (Chowienczyk et al. 1992), smoking (Celermajer et al. 1993; Adams et al. 1997), diabetes, obesity (Walther et al. 2004) and physical inactivity (Thijssen et al. 2008). These pathophysiological stimuli provoke vascular injury by upsetting normal regulatory properties of the endothelium via a reduction in the bioavailability of endothelium-derived NO (Rubanyi 1993; Anderson 1999) and by rapid catabolism of available NO by reactive oxygen species to peroxynitrite and hydrogen peroxide that further amplify vascular oxidative stress (Cohn et al. 2004). Endothelial dysfunction may involve an imbalance between relaxing and contracting factors, between pro- and anti-thrombotic factors, or between growth-promoting and inhibitory factors (Rubanyi 1993).

Endothelial dysfunction is one of the earliest events in the pathogenesis of cardiovascular disease and is widely regarded as a necessary first step in the development of atherosclerosis (Ross 1993; Rubanyi 1993). Indeed, endothelial function has been shown to be a major prognostic tool. For example, Al Suwaidi et al. (2000) measured coronary artery endothelial function in 157 patients with coronary artery disease. Only participants showing the lowest tertile of coronary responses to acetylcholine experienced cardiovascular events. It has been shown that
Atherosclerosis in the peripheral vasculature (brachial artery) is significantly correlated with disease presence and severity in the coronary and carotid arteries (Sorensen et al. 1997). Furthermore, studies have also shown that endothelial function in peripheral vasculature shows strong prognostic value in individuals with cardiovascular risk factors (Mancini 2004). Neunteufl et al. (Neunteufl et al. 2000) showed, in five years of follow-up with patients with chest pain who underwent coronary angiography, that those with impaired brachial artery reactivity were more likely to undergo surgery than those with normal flow-mediated dilation. To investigate whether improvement in endothelial dysfunction predicts improved long-term outlook Modena et al. (2002) studied 400 postmenopausal women with hypertension. Brachial artery FMD was measured before and six months following normalization of blood pressure (Modena et al. 2002). Event rates were seven times higher in women who improved FMD by <10% compared to those who improved FMD by >10%. These studies show that preservation of endothelial function and reversal of dysfunction is an important therapeutic goal.

Most cardiovascular disease events result from atherosclerosis (Grey et al. 2003), a disease process originating in the walls of arteries manifested at an early stage in lesions known as “fatty streaks”, and later as advanced fibrous plaques that may impede blood flow and cause acute cardiac events (Ross 1993). In the intact endothelium, many of the protective functions are mediated by NO (Behrendt and Ganz 2002). Conversely, the dysfunctional endothelium that has reduced synthesis/release of NO, promotes the process of atherosclerosis (Rubanyi 1993; Alam et al. 2005) and thus has a significant effect on the long-term risk for cardiovascular disease (Leeson et al. 1997).

Atherosclerosis results from chronic minor endothelial damage that induces intimal hyperplasia and a chronic inflammatory state creating an atherosclerotic lesion (Munro and Cotran 1988). Nitric oxide is a free radical scavenger, and its reduced synthesis/release leads to the
existence of more superoxide anion radicals with greater ability to oxidize low-density lipoproteins (LDL) creating oxidized LDL (Rubanyi 1993). Oxidized LDL is a key component in endothelial injury (Ross 1993). Once formed, oxidized LDL may directly injure the endothelium and play a role in the increased adherence and migration of monocytes into the intima. Here monocytes may be converted to macrophages by oxidized LDL and other atherogenic substances (Ross 1993). The macrophages then incorporate oxidized LDL and turn into foam cells (Munro and Cotran 1988; Ross 1993). Platelets, endothelial cells, and macrophages release growth factors which promote smooth muscle cell proliferation and migration (Munro and Cotran 1988). Macrophages and proliferating smooth-muscle cells synthesize extracellular matrix proteins that, over a period of decades, lead to the development of an atherosclerotic plaque (see figure 1) (Munro and Cotran 1988). By losing its protective properties and allowing the unopposed action of atherogenic factors on the vessel wall, endothelial dysfunction is a major promoter of atherogenesis and thrombosis and consequently, cardiovascular events (Behrendt and Ganz 2002).

6.4. Exercise and the endothelium

Various pharmacological interventions such as ACE inhibitors, L-arginine supplementation, and smoking cessation have been shown to improve endothelial function in a variety of cardiovascular disease states (Moyna and Thompson 2004). Regular exercise represents a non-pharmacological option to maintain or improve endothelial dysfunction (Moyna and Thompson 2004). The repetitive augmentation of blood flow and shear stress brought about by regular exercise positively affects vascular reactivity. This improvement occurs in the form of up-regulation of NO bioactivity through increased protein expression of eNOS and enhanced phosphorylation of eNOS, resulting in overall enhanced vasodilation and attenuated vasoconstriction to vasoactive factors (Maiorana et al. 2003; Walther et al. 2004; Volker 2005). In addition to increasing eNOS
expression and phosphorylation exercise training positively affects NO half life by reducing NO
 degradation by reactive oxygen species (Walther et al. 2004).

Animal studies suggest that short-term exercise training enhances eNOS and NO
production and bioactivity, producing a short-term buffer to the increased shear stress of exercise
(Green et al. 2004). Following prolonged training, the increased production of NO and possibly
other mediators induces structural changes in the vessels resulting in an increase in lumen
diameter (Prior et al. 2003). This adaptation normalizes shear stress and endothelial NO activity
returns towards initial levels (Green et al. 2004). In animal models of pathological states including
hypercholesterolemia (Niebauer et al. 1999), hypertension (Yen et al. 1995), diabetes (Sakamoto
et al. 1998), and heart failure (Lindsay et al. 1992; Wang et al. 1997) there is evidence that
exercise training can improve NO-related endothelial function.

In humans, cross-sectional exercise studies have found both enhancement (Kingwell et al.
1996) and no difference (Taddei et al. 2000) in endothelial function between active and sedentary
young men. Similarly, longitudinal studies have shown that exercise training does (Clarkson et al.
1999) and does not (Kingwell et al. 1997b) significantly impact endothelial function when assessed
in healthy young men. However, exercise studies using clinical populations (i.e. those with
endothelial dysfunction) including individuals with heart failure (Hambrecht et al. 2000a), CAD
(Hambrecht et al. 2000c), or in the elderly (Taddei et al. 2000), all show that physical activity clearly
has a beneficial effect on endothelial function. This evidence suggests that a greater training load
may be needed to improve endothelial function in healthy, young individuals (Clarkson et al. 1999)
than in conditions associated with endothelial dysfunction or to combat the negative effects of
ageing (Green et al. 2004). Also, it appears that individuals with endothelial dysfunction respond
more rapidly to training than healthy individuals, with endothelial function improving after as little as
four weeks (Hambrecht et al. 2000b; Linke et al. 2001).
In terms of whether endothelial adaptations are local or systemic in nature, recent studies have shown that the vascular shear stress that accompanies whole body exercise training can enhance endothelial NO-related vasodilator capacity not only in the active muscle bed but also systemically (Green et al. 2002; Maiorana et al. 2003). Exercise training involving a large muscle mass causes HR and pulse pressure to increase, resulting in systemic increases in pulsatile flow and pulse pressure (Maiorana et al. 2003). Endurance exercise using the legs is shown to augment NO-mediated dilation in the untrained forearm (Kingwell et al. 1996). Additionally, these effects on the endothelium appear to extend to the coronary circulation (Hambrecht et al. 2000c).

6.5. **Endothelial dysfunction in SCI**

Research regarding endothelial function in SCI is lacking. A number of risk factors for cardiovascular disease and endothelial dysfunction have been demonstrated in individuals with SCI (Bauman et al. 1999a). These include hyperlipidaemia, hypertension, type II diabetes, and hyperinsulinaemia (Bauman et al. 1992; Bauman et al. 1999a) as well as diminished physical activity and/or aerobic fitness (Hoffman 1986b; Wecht et al. 2000; Wecht et al. 2003). Additionally, the volume and velocity of lower extremity circulation is much lower after SCI (Jacobs and Nash 2004). This circulatory hypokinesis (Hjeltnes and Vokac 1979) is a result of loss of autonomic control of blood flow and a decreased regulation of local blood flow by the endothelium (Nash et al. 1996; Jacobs and Nash 2004). Low venous compliance (Miranda and Hassouna 2000) as well as decreased volume and velocity are associated with an increased risk for venous thrombosis (Green et al. 1992; Jacobs and Nash 2004). It also appears that there are pathological haematological factors, such as abnormal platelet function (aggregability and release of atherogenic mitogens) in which the endothelium plays a main role, directly involved in atherosclerosis in the SCI population (Bauman et al. 1999b).
7. **Arterial Compliance**

When the aortic valve closes after ejection of SV, the decay of blood pressure prior to the next heart beat describes a waveform that depends on the compliance of the arterial system into which the blood is being delivered (Cohn 1998). The ratio of change in volume to change in pressure defines arterial compliance (Syeda et al. 2003). It signifies the ability of a vessel to store blood volume temporarily as it is ejected with each cardiac contraction (Cohn 1998; Glasser 2000). Higher values indicate a less stiff/more compliant vasculature.

7.1. **Measuring arterial compliance**

Measures of arterial compliance can be assessed with applanation tonometry, used to non-invasively obtain the arterial pressure waveforms for pulse wave analysis (Cohn et al. 1995; Hayward et al. 2002; Matthys and Verdonck 2002; Syeda et al. 2003). The arterial pressure waveform is created by the overlapping of two waves, a forward pressure wave of ventricular contraction and a reflected wave from the vascular periphery (McVeigh et al. 1999; Mackenzie et al. 2002). Applanation tonometry involves placing a tonometer over a superficial artery to minimally flatten (applanate) the arterial wall (Matthys and Verdonck 2002). In normalizing the circumferential stresses, the electrical resistance of a small piezoelectric crystal within the tip of the tonometer varies directly with intra-arterial pressure (Hayward et al. 2002). This allows for recording of the pressure waveform. Analysis of the pulse wave is accomplished through use of a modified Windkessel model of circulation, a well established electrical analog model that treats the arterial vasculature as a hydraulic filter converting pulsatile flow from the heart to steady flow in the capillaries during diastole (Cohn et al. 1995; Cohn 1998; McVeigh et al. 1999).
7.2. Arterial compliance physiology

The arterial system is composed of large elastic arteries and smaller muscular peripheral arteries. The wall of arteries consists of the adventitia, media, and intima, with a single layer of endothelial cells (see section 6) separating blood from the vessel (Volker 2005). Large arteries have much elastin and collagen and smaller arteries are rich in smooth muscle. Elastin fibres play an important part in determining vessel behaviour at lower pressures and collagen fibres play a larger role at higher pressures (Bank et al. 1996).

Large elastic arteries such as the aorta buffer the flow and pressure variation created by the left ventricle as it contracts and, as the Windkessel model describes, converts pulsatile flow to steady flow at the peripheries (McVeigh et al. 1999). This maintains continuous tissue oxygenation and decreases cardiac work. Elastic recoil of the central arteries in diastole is important for coronary perfusion and a loss of this elasticity impairs coronary flow and may contribute to coronary artery disease (Jani and Rajkumar 2006).

The determinants of change in compliance also differ between large, small, and resistance arteries. In large arteries, collagen and elastin are the determinants of function (Cohn et al. 2004). In smaller arteries (such as the radial artery) vascular smooth muscle function, mediated by the endothelium, plays a role in determining compliance and calibre. In resistance arteries, NO released from the endothelium penetrates the thin-walled arteries and is essential in determining calibre and compliance via its actions on smooth muscle (Vaughn et al. 1998; Cohn et al. 2004).

The velocity at which the pressure waveform travels through the vasculature is positively correlated with the stiffness of the vessel walls (Mackenzie et al. 2002). In elastic vessels, the reflected wave tends to arrive back at the aortic root during diastole; this increases diastolic pressure and therefore improves coronary artery perfusion (Mackenzie et al. 2002). In stiff arteries, the reflected wave travels faster and arrives back at the aortic root during systole. This causes an
increased systolic and decreased diastolic pressure (Mackenzie et al. 2002; Syeda et al. 2003). High central systolic pressures increase the workload of the heart, promoting ventricular hypertrophy, and low diastolic pressures reduce coronary artery perfusion (van Popele et al. 2001; Mackenzie et al. 2002).

Stiffening occurring in different parts of the vasculature (large conduit arteries, small arteries, and arterioles) will have a different effect on the appearance of the pressure waveform. Stiffening of the aorta and large conduit arteries accelerates pulse wave velocity and increases pulse pressure via increased systolic and decreased diastolic pressure (Beltran et al. 2001). Stiffening of small arteries will alter the timing and decay rate of reflections that change the contour of the pressure wave. Stiffening of arterioles results in an increase in mean arterial pressure (Cohn et al. 2004).

7.3. **Arterial compliance pathophysiology**

Endothelial dysfunction and the accompanying structural and functional changes in the arterial wall are the earliest markers of atherosclerosis and coronary artery disease (Hayoz et al. 1992; Cohn 1998). Inasmuch as this reduced function influences the tone of the arterioles, the increasing blood pressure and decreasing arterial compliance may be manifestations of the atherosclerotic process (Ross 1993; Cohn et al. 2004). Endothelial dysfunction occurs in the entire arterial system but is most easily identified in very small arteries and arterioles (Vaughn et al. 1998; Hypertension Diagnostics 2002). Changes in small artery elasticity may be due to structural or functional changes closely tied to endothelial dysfunction (Grey et al. 2003).

In recent years, researchers have used pulse wave analysis to show that arterial stiffness is associated with atherosclerosis (van Popele et al. 2001) and atherosclerotic burden, that is, compliance decreases as the amount and severity of atherosclerosis increases (Syeda et al.
Importantly, changes in the compliance of small and large arteries do precede (by years) the presence of plaques characteristic of atherosclerosis (Grey et al. 2003). These changes are important early predictors of the risk of cardiovascular disease events (Grey et al. 2003; Cohn et al. 2004).

Factors such as hypertension (Cohn et al. 1995; Grey et al. 2003), coronary artery disease (Grey et al. 2003), and diabetes (Grey et al. 2003), in addition to being endothelial dysfunction risk factors, are associated with a decrease in small artery compliance. Preliminary analyses also support the use of the modified Windkessel model in identifying individuals at risk for atherosclerotic events such as heart attack and stroke (Grey et al. 2003). Large artery compliance has also been shown to have a strong association with cardiovascular risk factors such as hypertension (Arnett et al. 2001; Waring et al. 2004). In many of the above mentioned risk factors, a dose response pattern has been observed, with the intensity of exposure to risk factors being predictive of vascular dysfunction (Waring et al. 2004). The evaluation of arterial compliance thus plays an important role in helping to identify those who are at increased risk for cardiovascular disease.

7.4. Arterial compliance in exercise

Cross-sectional studies have shown that endurance trained individuals have greater arterial compliance than matched controls (Cameron and Dart 1994; Kingwell et al. 1997a). Endurance-trained individuals also show an absent or attenuated decrease in arterial compliance with age (Tanaka et al. 1998; Tanaka et al. 2000).

Aerobic exercise has proven to be effective in increasing arterial compliance (Cameron and Dart 1994; Tanaka et al. 2000; Parnell et al. 2002). Exercise training studies have shown that the arterial compliance of otherwise-healthy sedentary individuals improves within a brief period of
aerobic exercise training (Tanaka et al. 2000) and even following an acute bout of moderate exercise (Cameron and Dart 1994). In the clinical setting, increases in arterial compliance (35%) in individuals with congestive heart failure have been documented following an eight week exercise program (Parnell et al. 2002).

There are several mechanisms through which improvements in arterial compliance are thought to occur. Since biochemical changes in the actual composition of the arterial wall are believed to occur over a period of years (Tanaka et al. 2000), changes in arterial compliance seen in short-term aerobic exercise studies must occur through other means. One possibility is that the increased pulse pressure and mechanical distention during exercise sessions stretch collagen fibres and modify their cross-linking, resulting in increased arterial compliance (Brue et al. 1998; Tanaka et al. 2000). Arterial compliance can also be altered via modulation of sympathetic-adrenergic tone of smooth muscle cells in the arterial wall (Boutouyrie et al. 1994). Thus, it is possible that regular exercise improves arterial compliance by reducing the chronic suppressive influence of the sympathetic-adrenergic tone either directly or by improving the sympathoinhibitory effect of NO.

7.5. Arterial compliance in SCI

Individuals with SCI show an increased prevalence for a number of cardiovascular risk factors (ACSM 2002; Wecht et al. 2004) associated with decreased arterial compliance (Wecht et al. 2004). A recent finding suggests that normotensive individuals with paraplegia exhibit decreased arterial compliance compared to able-bodied controls (Wecht et al. 2004). These findings were confirmed in a recent study by our research group in females with SCI (Zbogar et al. 2008). Functional electrical stimulation leg cycle ergometry exercise has been shown to have a beneficial effect on small artery compliance in persons with SCI (Zbogar et al. 2008). Further
research is warranted, since the detection of early vascular disease is essential for preventing, determining, and treating cardiovascular disease.

8. Quality of Life

There is consistent evidence that regular exercise improves fitness in individuals with SCI (Glaser 1985; Hoffman 1986a; Figoni 1990; Davis et al. 1991; Anderson 2004; Jacobs and Nash 2004). The importance of physical activity in SCI rehabilitation is continually gaining more recognition for its ability to promote functional independence (Hicks et al. 2003; Ginis and Hicks 2005) and decrease the risk of chronic disease (Noreau and Shephard 1995). Indeed, the vast majority of individuals with SCI believe that exercise is an essential part of rehabilitation (Anderson 2004). However, people with SCI remain among the most inactive segment of society (Ginis and Hicks 2005). Few individuals with SCI have the requisite fitness required to carry out activities of daily living and this negatively affects quality of life (QOL) (Noreau and Shephard 1995; Ginis and Hicks 2005). Quality of life has been defined by the World Health Organization as:

"individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." (1998)

Health-related quality of life (HRQOL) is an individual's satisfaction or happiness with domains of life insofar as they affect or are affected by health. HRQOL can be distinguished from quality of life as defined above in that it concerns itself primarily with those factors that fall under the purview of health care providers and health care systems (Wilson and Cleary 1995).

Generally speaking, then, assessment of HRQOL represents an attempt to determine how variables within the dimension of health (e.g., a disease or its treatment) relate to particular
dimensions of life that have been determined to be important to people in general (generic HRQOL) or to people who have a specific disease (condition-specific HRQOL). Most conceptualizations of HRQOL emphasize the effects of disease on physical, social/role, psychological/emotional, and cognitive functioning. Symptoms, health perceptions, and overall quality of life are often included in the concept domain of HRQOL (Ware 1995).

Most HRQOL instruments are considered objective approaches to QOL measurement. In the objective approach QOL is measured as a one's score on an index composed indicators of "the good things in life". The index is composed of underlying values that are generally those of society or the investigators only and are not made explicit. The index assumes that (1) the same domains of life are important to all people; (2) in each area, all people have the same needs and goals; and (3) happiness and satisfaction are directly proportional to the degree that these standard needs are satisfied and the goals met.

In contrast to the objective approach is the view that the quality of one's life can only be determined by the person living it. This subjective approach focuses on the individual's subjective view of QOL. Here QOL is defined as the reaction, either more cognitive or evaluative (life satisfaction) or affective (happiness, morale), to the congruence or discrepancy between a person's standards, goals, values, and his/her actual situation and accomplishments. This study included questionnaires from both approaches; some objective and others subjective in nature.

While many studies have investigated cardiovascular function in SCI, few have included measures of QOL (Hicks et al. 2003) despite the fact that research consistently shows that chronic exercise has beneficial effects on numerous subjective outcomes such as depression, self-concept, and QOL (Noreau and Shephard 1995; Hicks et al. 2003). This is an important issue to address. Although individuals with SCI are living longer (Glaser 1985; DeVivo et al. 1999), their QOL may remain low.
Studies comparing QOL in individuals with SCI compared to able-bodied individuals show that the average scores of SCI groups are significantly lower although the differences are not as large as might be expected (Dijkers 2005). Studies employing the Medical Outcomes Study 36-item Short Form (SF-36) (see Methods 8.2.2.3) expectedly show lower scores on Physical Functioning and Role Limitations Due to Physical Problems in the SCI population compared to able-bodied persons (Leduc and Lepage 2002; Post and Noreau 2005). Using other measures of QOL assessment, scores of mental health, vitality, and role limitations due to emotional problems and the mental dimension score are not lower in SCI than in the general population (Leduc and Lepage 2002; Post and Noreau 2005). Nevertheless, in general most studies show significantly lower QOL scores across domains in persons with SCI compared to the general population although these differences are not as large as expected (Post and Noreau 2005). Further research is warranted, since QOL is affected by SCI.

9. Research Methods

9.1. Participants

Eight asymptomatic paraplegics with SCI lesions of traumatic origin were recruited. Eight age-, gender-, and activity-matched able-bodied controls were recruited. Activity matching was facilitated via a physical activity assessment questionnaire which asks participants about physical activity frequency, intensity, duration, and mode (see Appendix B). Participant characteristics are presented in Table 1a-b. All participants were between the ages of 18-46 and were asymptomatic, non-smokers, not currently using medications that would affect their autonomic, cardiovascular, respiratory, or metabolic responsiveness to exercise. We attempted to restrict the participant population to individuals with a lesion between the sixth and twelfth thoracic neurological level (T6-
T12) and with at least one year elapsed since time of injury. Above the T6 level, lesions may affect sympathetic stimulation to the heart; including these individuals would cause a large variation in exercise response. Participants with SCI were assessed via the American Spinal Injury Association (ASIA) classification of spinal cord injury (see Appendix E). We attempted to recruit individuals with grade A or B on the ASIA impairment scale. Improvement or recovery from SCI largely occurs in the first 6 months after injury and is complete by 2 years (McDonald et al. 2002). The literature shows that those individuals with an ASIA Grade A SCI do not recover by more than one grade 2 years after injury. In individuals with incomplete SCI small improvements may occur after 2 years (McDonald et al. 2002). Thus, if study participants had been recently assessed (within 1 year) with the ASIA classification that grading was used. These selection criteria were applied to decrease the variable exercise responses of including participants having different aetiologies, types and levels of spinal injury (Lassau-Wray and Ward 2000; Jacobs and Nash 2004).

Autonomic dysreflexia is a serious condition occurring in those with an SCI lesion at or above T6. Autonomic dysreflexia is rarely seen in individuals with lesions below T6 and when it occurs the reaction is often milder (Blackmer 2003). It results from noxious stimuli to intact sensory nerves below the level of injury which leads to relatively unopposed sympathetic outflow and acute hypertension. Parasympathetic outflow from the vagus nerve causes reflexive bradycardia, but this is insufficient to offset the widespread vasoconstriction (Blackmer 2003). Individuals with SCI were asked if they experience autonomic dysreflexia. These individuals were excluded from the study as exercise is a known cause for autonomic dysreflexia (Jacobs and Nash 2004). All participants were instructed to perform their bowel and bladder emptying routines prior to all tests. Bladder and bowel distention are the first and second most common causes of autonomic dysreflexia, respectively. Blood pressure was monitored at the conclusion of every exercise stage. Additional
exclusion criteria included ischaemic heart disease, unstable angina, dysrhythmia, recent osteoporotic fracture and tracheostomy (Hicks et al. 2003).

Common medications used by individuals with SCI in the non-acute period of injury deal with pain and spasticity as well as bowel and bladder dysfunction. Pharmacological agents used to treat neuropathic pain include anti-epileptic drugs such as Gabapentin (Neurontin) and Carbamazepine (Tegretol) and tricyclic antidepressants such as amitriptyline (Elavil), doxepin (Sinequan), and mirtroptpyline (Pamelor). For the treatment of musculoskeletal pain muscle relaxants and nonsteroidal anti-inflammatory drugs are used. Medications used to treat spasticity include GABA\textsubscript{B} agonists (Baclofen), GABA\textsubscript{A} agonists such as diazepam (Valium), alpha 2-adrenergic agonists such as clonidine (Catapress) and tizanidine (Zanaflex), datroline sodium (Dantrium), nerve blocks with injections of phenol or absolute alcohol, and botulinum toxin. Medications dealing with bowel management include stool softeners such as docusate sodium (Colace), bulkforming agents, stimulants (Senna), and contact irritants such as bisacodyl (Dulcolax, Magic Bullet, Theravac, Fleets) and glycerin suppositories. Many of these can be started initially after the injury and gradually be discontinued. Others may be used occasionally when problems develop. Bladder medications fall in the classes of anticholinergics (oxybutynin, tolteridine, and propanthelene) and alpha adrenergic blockers (tamsulosin, terazosin, doxazosin, prazosin) (Sceiza and Shatzer 2003). Medications being taken by participants and their potential cardiovascular side-effects were recorded (see Table 2).

Control participants were recruited via advertisements on the University of British Columbia campus. Individuals with SCI were recruited primarily through the G.F. Strong Rehabilitation Centre Spinal Cord Program.
9.2. Testing Procedure

Each group participated in two testing days at the Cardiovascular Physiology and Research Laboratory at the University of British Columbia. On the exercise testing day each participant signed an informed consent form outlining the experimental procedures and a PAR-Q form. Measurements obtained on the exercise testing day consisted of the assessment of oxygen consumption, cardiac output, and peripheral muscle function during incremental exercise. The vascular assessment day consisted of the assessment of endothelial function, arterial compliance, the participants' health status, and QOL.

9.2.1. Exercise Measures

9.2.1.1. Arm Crank Ergometry Protocol

Participants were seated at the electronically braked arm ergometer (Ergometrics er800SH, Ergoline, Germany). The participant and ergometer were positioned such that the axis of the crank arm was set to shoulder height and the elbows slightly flexed at the point of furthest reach. Data collection began with 8 min of baseline measurements of blood pressure, oxygen consumption (via mass spectroscopy), cardiac function (via ECG and acetylene rebreathing), and peripheral muscle oxygenation and utilization (NIRS and acetylene rebreathing). Individuals with SCI had their height measured in the supine position resting on a plinth. Able bodied individuals had their standing height measured. Body weight was obtained using a scale capable of accommodating a wheelchair (Seca 684, CA, USA).

Following the 10 minutes of baseline measures, arm crank ergometry commenced. This exercise test consisted of 3-minute stages of exercise beginning at a power output of 10-15 watts and increasing 10-15 Watts per stage until the participant reached volitional fatigue. Each 3 minute stage was concluded with a 60 second recovery period, the purpose being to provide a time
interval in which to collect haemodynamic measurements without motion artefact (Franklin 1985). This protocol is valid as studies examining the physiological responses to continuous versus intermittent arm exercise protocols show that significant differences do not exist between the VO$_2$max attained via these protocols (Sawka 1986). While changes in central haemodynamics occur immediately upon cessation of arm exercise (Miles et al. 1984), in this study all measures were obtained during exercise except for blood pressure which can not be obtained during arm ergometry and was obtained during the rest period between stages. Exercise tests were to be terminated immediately if one or more of the following symptoms occurred: 1) chest pain, 2) ST segment depression or elevation of > 1mm, 3) a significant decrease in systolic blood pressure during exercise (>10 mmHg), and/or 4) other abnormal ECG responses. Once participants completed their test they entered a 2 minute active rest period where they continued to exercise at approximately 30-40% of their maximal wattage. Following active recovery a passive recovery period of 4 minutes began. Measures of HR and blood pressure were taken as the participants recovered.

9.2.1.2. Exercise Measurements

Expired gas and ventilatory parameters were acquired throughout the incremental arm ergometer test using a mass spectrometer (Amis 2000, Innovision, Odense, Denmark) allowing for the determination of submaximal and maximal oxygen consumption. Continuous measurements of HR (3-electrode ECG) and oxyhaemoglobin saturation (SaO$_2$) were obtained. Oxygen saturation was measured by a pulse oximeter (Ohmeda Biox 3740, Louisville, CO) at the pinna of the ear. Values were averaged and recorded every second.

Peripheral muscle (biceps brachii and vastus lateralis) oxygenation was assessed non-invasively using a fast spatially resolved NIRS (NIRO-300, Hamamatsu, Phototonics, Japan).
One set of optodes was positioned over the motor point of the medial aspect of the biceps brachii, approximately 6-8 cm from the elbow crease of the right arm. Another set of optodes was placed on the distal portion of the right vastus lateralis. The optodes were affixed in a probe holder that ensures maintenance of distance between the emission and detection probes. The limb was wrapped with black lycra followed by tensor bandages to stabilize the probes and prevent ambient light from contaminating the NIRS signal. Changes in oxygenated and deoxygenated haemoglobin were calculated by measuring light attenuation at 775, 810, 850, and 910nm wavelengths and analyzed with an algorithm using the modified Lambert-Beer law. The combination of oxygenated and deoxygenated haemoglobin, total haemoglobin, is presented as the degree of muscle blood flow (Bousshel et al. 2001). Changes in haemoglobin were calculated relative to resting levels. The NIRO 300 was calibrated prior to each test. A running average integrated over 10 seconds was used.

A data acquisition system (Powerlab 16/30, ADInstruments, Colorado Springs, CO) and personal computer was used to record continuous ECG, HR, SaO2, and NIRS data.

At every third minute of the resting period and during the third minute of each three-minute exercise stage, measures of Q were assessed non-invasively using inert gas rebreathing (Amis 2000, Innovision, Odense, Denmark). During the 1 minute rest interval between exercise stages participants had their blood pressure measured on the arm and indicated their rating of perceived exertion using the modified Borg scale (see Appendix D).

9.2.2. **Resting Measures**

As with other physiological tests, arterial compliance and endothelial function may be affected by several factors. As vascular function appears to follow the same diurnal pattern as blood pressure (Hypertension Diagnostics 2002) measurements were taken in the morning
between 8:00 and 11:00 AM for all participants. To help control for dietary effects, participants were asked to fast overnight (8 hours). Participants were also be asked to empty their bladder, to refrain from vigorous exercise, smoking, drinking alcoholic or caffeinated beverages, and taking vitamin supplements at least 8 hours prior to testing. A certified ultrasonographer performed all brachial artery diameter and flow measurements.

9.2.2.1. Arterial Compliance

The non-invasive assessment of large and small arterial compliance was performed using the HDI/Pulse Wave CR-3000 Cardiovascular Profilor (Hypertension Diagnostics/Pulse WaveTM CR-3000). This technique, involves 30-second recordings of signal-averaged arterial pulse waves by applanation tonometry using a surface-residing transducer over the radial pulse of supine subjects (Resnick et al. 2000). The transducer flattens (aplanates) the vessel and produces a measurable pressure waveform (Hayward et al. 2002; Matthys and Verdonck 2002). The waveform is calibrated by the oscillometric method with a cuff on the opposite arm and a calibration system internal to the HDI/Pulse Wave CR3000 CV Profilor (Schillinger et al. 2002). The accuracy of this method of obtaining waveforms has been validated in animal and human studies (Hayward et al. 2002). A computer-based assessment of the diastolic pressure decay using a modified Windkessel model of the circulation separates diastole into two components: large artery compliance (capacitance), measured as the exponential decay of the waveform and small artery compliance (oscillatory) measured as the fluctuations in the waveform that occur on the basic shape of the waveform (McVeigh et al. 1999; Arnett et al. 2001). The CVProfilor® (MD-3000 cardiovascular profiling system, Eagan, MN) used in this study provides a global compliance measure (Pannier et al. 2002). It uses the modified Windkessel model to provide an independent assessment of capacitive compliance (C1), reflecting large conduit arteries, and oscillatory (or reflective)
compliance (C2), reflecting smaller, more peripherally located arteries and arterioles (Finkelstein and Cohn 1992). The CVProfilor® has proven to be a useful tool in identifying individuals at risk for atherosclerotic events (Grey et al. 2003). The C2 index identifies the presence of endothelial dysfunction in the microvascular circulation (McVeigh et al. 2001; Hypertension Diagnostics 2002). The C1 index identifies stiffness and atherosclerosis of the aorta and large arteries. In general, the C2 index is more sensitive and shows a decrease in arterial elasticity before the C1 index (Hypertension Diagnostics 2002; Cohn et al. 2004).

Measurement of arterial compliance commenced following 5 minutes of supine rest. Measures were taken in triplicate and the closest two values were averaged. The mean coefficient of variation for large and small artery compliance was 0.05 and 0.10, respectively.

9.2.2.2. Endothelial Function

Endothelial function was assessed non-invasively via FMD. Subjects lay supine in a quiet, temperature-controlled room for 10 minutes to allow for blood pressure stabilization. Three monitoring ECG electrodes were attached to the chest. A 7.5MHz linear array transducer attached to an ultrasound machine (Logic i, GE Medical Systems, Wauwatosa, WI, USA) was used to image the brachial artery in a longitudinal section approximately 5 cm proximal to a blood pressure cuff which was attached on the forearm just below the antecubital fossa. Upon obtaining a baseline value for brachial artery diameter and blood velocity, the cuff on the forearm was inflated to 300mmHg for 5 minutes. Following cuff deflation hyperaemic flow velocity in the brachial artery was recorded for 25 seconds followed by continuous measurement of brachial artery diameter for 3 minutes. After a resting period of 15 minutes, baseline measures of brachial artery diameter were again recorded. Then a systemic dose of nitroglycerin (0.3 mg tablet) was administered sublingually to measure endothelium-independent vasodilation (Higashi et al. 2001; Komai et al.
or nitroglycerin mediated dilatation (NMD). Continuous measurements of brachial artery diameter were taken for 6 minutes following nitroglycerin administration. Data collected during these measurements was saved to DVD for analysis offline.

Offline vessel diameters of the brachial artery were measured at baseline and from 45-180 seconds after cuff release and for 6 minutes following NTG administration. All measures were taken at the end-diastolic phase of the cardiac cycle for each heart beat. Five measures of vessel diameter were taken and averaged for every cardiac cycle. FMD was reported as the greatest increase in end-diastolic diameter from baseline averaged from the 3 highest consecutive recordings. FMD and NMD were expressed as the maximal absolute value, percent change from baseline, and as a FMD/NMD ratio (Chan et al. 2003).

9.2.2.3. Quality of Life Indicators

To provide insight into psychological well-being five questionnaires were employed (see Appendix A):

The Rosenberg Self Esteem Scale (SES) is a subjective self-report measure of global self-esteem. It consists of 10 statements related to overall feelings of self-worth or self-acceptance. Cronbach’s alpha for this scale is reported at 0.86 (Vermillion and Dodder 2007).

The Satisfaction with Life Scale (SWLS) allows individuals to assess their well-being based on their own unique criteria without reference to a specific domain. Among the well-being scales, the SWLS has been used most often with the SCI population (Richards et al. 1999). The SWLS is a subjective questionnaire comprised of 5 items rated on a 7-point Likert scale and has been shown to have desirable psychometric properties with a coefficient alpha of 0.87 and correlation coefficient of 0.82 (Diener et al. 1985).
The Centre for Epidemiological Studies Depression Scale (CES-D) measures the frequency of 20 depressive symptoms over the past week. Responses are made on a 4-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). Attainable scores on the scale range from 0-60. Scores of 16 or greater indicate increased risk for clinical depression. With respect to reliability, in the SCI population the CES-D has been shown to have a Cronbach's alpha of 0.91 and retest reliability of ICC=0.87 (95% confidence interval (CI) 0.79–0.93) (Miller et al. 2008).

The Medical Outcomes Study 36-item Short Form (SF-36) is the most validated health related QOL questionnaire. The SF-36 has been shown to have a good internal consistency (Cronbach's alpha coefficient 0.72–0.98) and intrainterviewer reliability (ICC= 0.71–0.99) (Lin et al. 2007). The SF-36 is an objective questionnaire that consists of 36 items in 8 scales (General Health, Physical Functioning, Pain, Social Functioning, Role Limitations due to Physical Problems, and Role Limitations due to Emotional Problems, Mental Health, and Vitality) that can be clustered in 2 summary scores for physical and mental health. Designed for use in various diagnostic groups, the SF-36 has been used in persons with SCI (Post and Noreau 2005). Though its use in individuals with SCI has been rated as moderately positive (Andresen et al. 1999) the physical functioning scale has been found to be offensive to individuals with mobility impairments as half the items make reference to walking or climbing (Andresen et al. 1999).

The World Health Organization Quality of Life assessment (WHOQOL-BREF) is a subjective short form assessment designed to provide information on 4 domains including physical health, psychological health, social relationships, and environment (WHO 1996). The WHOQOL-BREF has proven to be an appropriate generic health-related quality of life measure for persons with traumatic spinal cord injuries. In this population the WHOQOL-BREF has been shown to have
a Cronbach's alpha coefficient of 0.75-0.87 and with respect to intrainterviewer reliability an ICC of 0.84-0.98 (Lin et al. 2007).

10. **Statistical Analysis**

For both exercise and measurement of vascular function, data was analyzed off line for each participant. Results were considered significant at an alpha of $p \leq 0.05$. Tukey post-hoc comparisons were conducted when significant differences were observed. Statistical analyses were performed using SPSS 16.

Comparisons for exercise measures were made between individuals with SCI and able bodied individuals via 2-way (2x6) mixed model ANOVA. The independent variables include one between-subjects variable with 2 levels (individuals with SCI, able-bodied individuals) and one within-subjects variable with 6 levels (0, 20, 40, 60, 80, and 100% watts).

Measurement of large artery compliance, small artery compliance, flow mediated dilatation and nitroglycerin mediated dilatation were analyzed via 1-way between-groups ANOVAs. The independent variable for each ANOVA is a between-subjects variable with 2 levels (individuals with SCI and able-bodied individuals).

All questionnaires were analyzed via independent-samples t-test.

11. **Results**

11.1. **Participants**

Eight able-boded individuals and 8 individuals with SCI participated in the study. There were no adverse events in response to the exercise test or the measurement of endothelial function. We attempted to include only those participants with a lesion level between T6-T12.
However, we were able to include one participant with a T5 lesion as she never experienced autonomic dysreflexia and had a normal HR response to exercise. Another participant with an incomplete T12 lesion who did not use a wheelchair but instead ambulated with the assistance of a cane participated in the study. This participant was excluded from analyses because of their ability to walk, which was not representative of the SCI group and would confuse the investigation of differences between groups in this study. Moreover, the age and gender matched control was an inadequate match for the very high activity level of this individual and was excluded from analysis. Therefore fourteen participants were left for inclusion in the analyses. There were no significant differences between individuals with SCI and able-bodied individuals for sex, age, BMI, or activity level (see Table 1a, b). However individuals with SCI (M=123, SD=8.35) had a significantly higher resting systolic blood pressure than able bodied individuals (M=110, SD=9.09; t(12)=2.82, p=0.016, eta squared= 0.40). The same holds for diastolic blood pressure with individuals with SCI (M=71, SD=5.96) significantly higher than able-bodied individuals (M=63, SD=5.14; t(12)=2.72, p=0.019, eta squared= 0.38).

11.2. Exercise Measures

Maximal power output was not significantly different between individuals with SCI (M=69.29, SD=18.36) and able-bodied individuals [M=80.00, SD=26.93, F(1,12)=0.757, p=0.401; eta squared= 0.059]. A mixed model ANOVA was used to examine differences in relative and absolute VO₂, HR, SV, Q, avDO₂, and NIRS measures of blood flow and oxygenation in the arm and leg between individuals with SCI and able-bodied participants at stages of 0, 20, 40, 60, 80, and 100% of maximal exercise.

There was no statistically significant group by stage interaction for relative and absolute VO₂, HR, SV, Q, and avDO₂. Also there was no significant main effect for group for any of the
same variables. However effect sizes for all these variables, save avDO₂ were moderate to large. Differences between groups grew with able-bodied individuals increasing to a greater degree at 80 and 100% watt stages for VO₂ and Q (see Figure 2a, b, e). Individuals with SCI had a higher HR than able-bodied individuals at every stage, but results were non significant (see Figure 2c). The opposite holds for SV, with able-bodied individuals being higher at every stage. However the large amount of variability precluded statistically significant results (see Figure 2d).

There was a statistically significant main effect for exercise stage for all variables (refer to Figure 2a-e; see Table 3 for means and standard deviations). Specifically, for VO₂, HR, and Q, each stage was significantly higher than the preceding stage (see Figure 2a, b, c, e). For SV the 100% watts stage was significantly higher than values at 60% watts (see Figure 2d). For avDO₂ all exercise stages were significantly higher than 0% watts (see Figure 2f).

There was no statistically significant group by stage interaction for NIRS measures of total haemoglobin and oxygenation in the arm and leg between individuals with SCI and able-bodied participants. There was a significant main effect for group in leg oxygenation (see Figure 3c) with able bodied individuals having statistically significant lower oxygenation values at 40, 60 80, and 100% watt exercise stages compared to individuals with SCI. Though non-significant, able bodied individuals had consistently lower arm oxygenation values than individuals with SCI at all stages. Able-bodied individuals experienced higher values of change in total haemoglobin at all stages, and while statistical significance was not achieved (see Figure 3b) there was a large effect size (eta squared= 0.16).

There were statistically significant main effects for exercise stage for total haemoglobin and oxygenation in both the arm and leg. Specifically, for leg oxygenation (see Figure 3c), the 80 and 100% watt exercise stages were significantly lower from rest, all other exercise stages, and the 100% watt stage was significantly lower than the preceding 80% watt stage. Arm oxygenation
decreased from baseline until the 60% watt stage before increasing slightly during the 80 and 100% watt stages (see Figure 3a). Values of arm oxygenation for all exercise stages were significantly different from rest but not each other. For total haemoglobin in the arm there was a statistically significant trend of total haemoglobin increasing with exercise stage (see Figure 3b). For leg total haemoglobin there was a statistically significant trend of decreasing total haemoglobin with exercise stage (Figure 3d).

11.3. **Resting Measures**

11.3.1. **Arterial Compliance**

A one-way between-groups ANOVA was conducted to explore differences between individuals with SCI and able-bodied controls for large and small artery compliance. Means and standard deviations are presented in Table 4 and 5. There was no statistically significant difference between individuals with SCI ($M=19.59$, $SD=6.74$) and able-bodied individuals ($M=23.93$, $SD=10.35$, $F(1,12)=0.865$, $p=0.37$; eta squared= 0.07) for larger artery compliance (see figure 5). There was a statistically significant difference for small artery compliance [$F(1,12)=5.46$, $p=0.04$; eta squared= 0.31] with able-bodied individuals ($M=10.51$, $SD=1.69$) exhibiting higher values than individuals with SCI ($M=6.91$, $SD=3.70$) (see Figure 4).

11.3.2. **Endothelial Function**

A one-way between-groups ANOVA was conducted to explore differences between individuals with SCI and able-bodied controls for FMD, NMD, and FMD/NMD ratio. There was no statistically significant difference between groups for FMD [$F(1,12)=0.00$, $p=1.0$; eta squared=0.00], NMD [$F(1,12)=0.22$, $p=0.65$; eta squared=0.02], or FMD/NMD ratio [$F(1,12)=0.75$, $p=0.40$; eta squared=0.06]. Refer to Table 5 for means and standard deviations.
11.4. Questionnaires

Independent samples t-tests were conducted to compare individuals with spinal cord injury to able-bodied individuals in quality of life via the following questionnaires: the SES, the SWLS, the CES-D Scale, the mental component of the SF-36 and the WHOQOL-BREF.

There was no significant difference in self esteem between individuals with SCI (M=25.00, SD=5.48) and able bodied individuals (M=25.57, SD=3.60; t(12)=-0.231, p=0.82). The magnitude of differences in the means was very small (eta squared= 0.004).

There was no significant difference in satisfaction with life between individuals with SCI (M=25.00, SD=7.51) and able bodied individuals (M=28.14, SD=5.55; t(12)=-0.89, p=0.39). The magnitude of differences in the means was moderate (eta squared= 0.058).

There was no significant difference in depression between individuals with SCI (M=12.57, SD=12.04) and able bodied individuals (M=6.71, SD=3.90; t(12)=1.22, p=0.24). The magnitude of differences in the means was large (eta squared=0.10).

There was no significant difference in the mental health component of the SF-36 between individuals with SCI (M=74.57, SD=22.59) and able bodied individuals (M=83.29, SD=6.26; t(12)=-0.984, p=0.345). The magnitude of differences in the means was moderate (eta squared= 0.069). The physical health component of the SF-36 was not scored as individuals with SCI had varying interpretations or did not answer questions which required the individual to be able to walk.

While able bodied individuals scored higher in all four domains of the WHOQOL-BREF, physical and psychological health, social relationships, and environment, there was no statistical difference in physical health [t(12)=-2.01, p=0.07; eta squared=0.25], psychological health [t(12)=-1.08, p=.30; eta squared=0.09], social relationships [t(12)=-1.84, p=0.09; eta squared=0.21], and environment [t(12)=-0.46, p=0.66; eta squared=0.02].
Two individuals with SCI in this investigation were on antidepressant medications at the time of data collection (see Table 2).

12. Discussion

12.1. Exercise Measures

12.1.1. Cardiorespiratory Measures

Spinal cord injury can result in two major exercise-related problems: a reduced ability to voluntarily perform aerobic exercise using large muscle groups and an inability to stimulate the autonomic and cardiovascular systems to support higher levels of aerobic metabolism. Despite these limitations, in this investigation maximal power output was not significantly different between groups. Most exercise studies show that able-bodied individuals have a higher maximal power output than individuals with SCI (Davis 1993) although individuals with low lesion levels can have maximal power outputs similar to able bodied persons (Flandrois et al. 1986). In this study, able bodied individuals had a maximal power output 10 watts higher, a trend which supports the finding for higher power output in able-bodied persons. The lack of statistical significance is likely the result of high variability and also due to all SCI participants in the study having lesions below T5, the result being full function of the arms and an intact sympathetic innervation to the heart resulting in a more normal exercise response. Furthermore, some of the decrement in performance resulting from paralyzed trunk and leg muscles could be weighed against local muscle adaptations individuals with SCI obtain from using the arms to ambulate and exercise. Also, most of the able-bodied participants if and when they trained aerobically did not do so using the arms.

The VO$_2$max for arm ergometry in this study is comparable to values previously reported for able bodied individuals and those with SCI (Flandrois et al. 1986; Hopman et al. 1993a; Haisma
Equality of aerobic power between individuals with and without SCI who possess similar levels of physical activity has rarely been demonstrated (Davis 1993). However this investigation did not reveal differences in aerobic power between groups (see Figure 2a, b). The small sample size (n=14) may explain why significant differences were not observed. The tendency for higher (but non-significant) values in the last 2 exercise stages (see Figure 2a, b) and a large effect size (eta squared= 0.14) suggest that differences would be demonstrated with more participants. For example Hooker et al. (1993) found significant differences for VO2peak between 15 able bodied participants and 13 and 14 high and low lesion paraplegics, respectively (Hooker et al. 1993). Hopman et al. (1992) found significance difference for VO2peak with 11 able bodied and 11 paraplegic participants (Hopman et al. 1992). A power calculation (alpha=0.05, power=0.80) for this study indicates that a total of 34 participants would yield statistical significance.

In able bodied individuals, exercise of an aerobic nature results in peripheral arteriolar dilatation and pumping action of the skeletal muscle. This causes a shift in blood volume, with an expansion of central blood volume and augmented cardiac output and stroke volume (Tschakovsky et al. 1996). In individuals with SCI damage to sympathetic vascular muscle innervation in the legs and a loss of the muscle pump during activity causes venous dilatation and pooling of blood in the paralyzed legs and splanchnic area (Hopman 1994; Phillips et al. 1998). This causes a reduced circulating blood volume and preload to the heart resulting in a reduced SV (Jacobs and Nash 2004; Myers et al. 2007). This reduced SV is most noticeable in individuals with high lesions. Individuals with lower lesions are better able to maintain venous return due to an intact sympathetic innervation to the splanchnic area. However, a smaller SV at rest and exercise has also been seen in individuals with lesions below T6 relative to able bodied persons (Phillips et al. 1998; Schmid et al. 1998; Jacobs and Nash 2004). The results of the present investigation saw able bodied individuals with a higher SV at rest and at all exercise stages, which is in accordance with the
findings of others (Phillips et al. 1998; Jacobs and Nash 2004). However the large amount of variability precluded statistically significant results (see Figure 2d). A large to moderate effect size (eta squared= 0.10) suggests that statistical significance would be attained with more participants. A power calculation (alpha=0.05, power=0.80) indicates that a total of 28 participants would yield statistical significance.

Because of the lower SV often observed in SCI, there must be an increase in HR if Q is to be maintained. Figure 2c shows that HR was lower in able bodied individuals at all stages although results were non-significant. These trend supports the findings of others (Kinzer and Convertino 1989; Hopman et al. 1993a), and likely results from a less efficient redistribution of blood from the inactive lower body to the heart in individuals with SCI (Hopman et al. 1992). Figure 2c (and figure 2d) also shows that the mode of Q increase was the same in both groups, i.e. due to an increase in HR while the there was a small increase in SV. Importantly, the highest SV was achieved during maximal exercise. This would seem to indicate the basically normal regulation of the heart in individuals with spinal lesions below T5; however we did not measure parameters such as filling and compliance of the heart.

Although Q was not significantly different between groups (Figure 2e) there was a trend evidenced by a moderate effect size (eta squared= 0.08) for Q to increase to a greater level in able bodied participants during the higher stages of exercise. Moreover, a higher HR compensated for a decreased SV until the final stages. To discuss these findings in the context of previous work in the field, several studies (Hopman et al. 1992; Hopman et al. 1993a; Hopman 1994; Jacobs and Nash 2004) have found that during upper body exercise, individuals with paraplegia with intact sympathetic innervation of the heart demonstrate, at a given submaximal VO₂, similar Q compared with able bodied persons. However, SV and HR at these similar submaximal work levels are markedly different, with individuals with SCI having lower stroke volume and higher HR values at
low, moderate and high exercise intensities (Hooker et al. 1993; Hopman 1994). Though non-significant, the trends in our data support these findings of a lower SV and higher HR in SCI. The finding of a lower Q in SCI near and at maximal exercise (figure 2e) suggests that individuals with SCI have a central limitation compared to able bodied individuals. While non-significant, this finding supports those of most studies investigating central and peripheral adaptations in SCI that individuals with SCI have difficulty in inducing a volume load during arm ergometry (Jacobs and Nash 2004). This is likely in part due to impaired sympathetic outflow and impaired peripheral vasoconstriction and muscle pump of non-exercising tissue, leading to a decreased venous return and cardiac filling pressure (Myers et al. 2007).

At rest, oxygen extraction is approximately 23%. As exercise reaches VO$_2$max around 80 to 85% of available oxygen is extracted from the blood which results in an increased avDO$_2$ (Saltin 1985; Daussin et al. 2007). Arteriovenous oxygen difference in this study (Figure 2f) also increased significantly in both groups from rest to exercise as muscle metabolism increased and the need for oxygen in working muscle increased. However, avDO$_2$ plateaued for both groups in the early stages of exercise. Thus the increase in VO$_2$ seen above 40% of maximal wattage is not attributable to an increase in avDO$_2$. The implication here is that either the maximal ability of the muscle to take up oxygen had been attained early in the exercise test or that after a certain point additional oxygen extraction was not required. However, we know that limb blood flow is adjusted at a given power output to be above or below the normal blood flow level in relation to the deviation in CaO$_2$ as a result of varying PaO$_2$. (Welch 1982; Saltin et al. 1998) This suggests that the variable that is controlled is oxygen delivery and muscle blood flow is then the means by which it can be adjusted (Saltin et al. 1998). Since skeletal muscle is able to accommodate a flow of 200ml lOOg$^{-1}$ min$^{-1}$ or more during whole body exercise, a Q of 50-60L min$^{-1}$ or more would be required to approach that potential flow in a muscle (Ekblom and Hermansen 1968). Normal values for Q in
highly trained endurance athletes are usually around 30L min⁻¹ (Blomqvist and Saltin 1983; Rowell 1986; Gledhill et al. 1994). As a result, it is likely that if more oxygen were required, blood flow could continue to increase since the limit of skeletal muscle blood flow would not be approached by participants in this study. In this study, total haemoglobin (a surrogate measure for blood flow) to the arm as measured by NIRS (figure 3b) did in fact continue to increase well after the plateau in avDO₂ which would seem to indicate that blood flow, determined by central factors, is not a limitation.

12.1.2. Near Infrared Spectroscopy

At rest skeletal muscle has a high vascular resistance. This is a result of adrenergic sympathetic stimulation which causes arteriole smooth muscle to vasoconstrict (Seals and Victor 1991). At the beginning of exercise initial vasodilation is believed to occur due to a withdrawal of sympathetic outflow to arterioles in the working muscles. As exercise progresses, vasodilation is maintained and increased by autoregulation. The high metabolic rate of the exercising muscle causes local changes such as decreases in oxygen tension and pH, and increases in CO₂ tension, NO, potassium and adenosine concentrations (Pearson and Vanhoutte 1993) which result in vasodilation if the arterioles of the working skeletal muscle. Also, more capillaries are opened during exercise in working muscle, contributing to the increased blood flow in working muscle. It is these processes which help to explain the increase in total haemoglobin with increasing workload in the arms of both groups in this study as seen in figure 3b. These findings agree with those of others investigating blood flow in arm ergometry (Ahlborg and Jensen-Urstad 1991a; Ahlborg and Jensen-Urstad 1991b).

Though non-significant, total haemoglobin in the arm was higher across stages for able bodied participants. A large effect size (eta squared= 0.16) suggests that the lack of significance
was due to a lack of power. A power calculation (alpha=0.05, power=0.80) for this variable indicates that the addition of 6 participants in each group would be needed to have total haemoglobin in the arm achieve statistical significance. This trend towards difference may reflect the fact that the redistribution of blood flow to the active muscles during exercise that normally occurs in ambulatory individuals is largely absent after SCI (Myers et al. 2007). It has been shown that at maximal exercise arm blood flow and arm oxygen uptake are significantly higher in rowers than in able bodied controls (Volianitis et al. 2004). This investigation shows the opposite trend with those who use their arms to train and ambulate (SCI) having a lower arm total haemoglobin than able bodied controls. Presumably any local muscular adaptations were countered by a lack of skeletal muscle pump and absent or insufficient venoconstriction to minimize peripheral vascular volume, causing insufficient venous return, and blunting SV (Myers et al. 2007).

While vascular resistance in working skeletal muscle decreases with exercise, vascular resistance to viscera and non-exercising muscle increases. This is a result of an increase in adrenergic sympathetic output to these areas and is necessary for the regulation of blood pressure during exercise. Several authors (Kinzer and Convertino 1989; Hopman et al. 1993b) have shown that, due to a loss of sympathetic vasoconstriction in the legs, blood redistribution from the lower limbs was impaired in those with SCI. Figure 3d shows that total haemoglobin did indeed decrease with exercise of increasing intensity. However, there was no significant difference between groups in change in leg total haemoglobin during the exercise testing. This seems to contradict the trend of a lower increase in total haemoglobin in the exercising arms of SCI participants as there was not a concomitant difference between groups (Figure 3d). However we should note that splanchnic blood flow was not accounted for, the nature of NIRS measurement prevents knowledge of absolute values which could be different between groups (de Groot et al. 2006).
The decrease in oxygenated haemoglobin in the arms (see figure 3a) from rest to the first 3 stages of increasing exercise intensity suggests a greater release of oxygen by haemoglobin via the Bohr effect. There is a levelling off of deoxygenation in the exercising arms observed in both SCI and able bodied participants from 60 to 100% of maximal wattage despite a continued increase in total haemoglobin (see figure 3b). These findings are similar to that found in other research investigating muscle deoxygenation during arm ergometry (Muraki et al. 2004) and suggests that the oxidative ability in the working muscle reached a limit, not that oxygen supply to the working muscle was inadequate. If muscle blood flow increased beyond the muscle metabolic requirement, the concentration of $O_2$Hb would be expected to increase due to a lower $O_2$ extraction (DeLorey et al. 2003). This suggests a peripheral limitation to exercise.

As exercise intensity progressed throughout the exercise test leg oxygenation decreased for both individuals with SCI and able bodied controls (Figure 3c). Concentration changes in oxygenation are dependent on the dynamics of the equilibrium between tissue $O_2$ demand and supply (Kawashima et al. 2005). Because the leg musculature was not being used for the exercise test, we may assume that $O_2$ demand did not increase in the vastus lateralis. Thus the decrease in leg oxygenation is believed to reflect a decreased supply of $O_2$ to the leg, a result of increased need of the exercising arms.

Able bodied participants experienced a significantly greater decrease in oxygenated haemoglobin in the leg during the exercise test than individuals with SCI (Figure 3c). A possible reason for this difference may lie with the muscle contractions that occur in the leg musculature as exercise intensity reaches higher levels. While all able bodied participants were asked to minimize movement of the legs during the test they likely did recruit their legs as stabilizers to increase leverage with exercise at higher wattages.
12.2. Resting Measures

This study indicates that individuals with SCI have poorer small artery compliance than able-bodied control participants (figure 4). This trend is in agreement with previous research that shows decreased arterial compliance in persons with paraplegia (Wecht et al. 2004; Zbogar et al. 2008). In individuals with SCI the extreme inactivity resulting from paralysis and the loss of supraspinal sympathetic vascular control are both cited as potential factors for poor arterial compliance in the leg (De Groot et al. 2005). Arterial compliance in this study was measured at the radial artery and not in the leg. However, the applanation tonometer used in this study provides a global assessment of arterial compliance, and not strictly the compliance of the local (radial artery) vasculature. This is because the tonometer employs a Windkessel model of the circulation where the diastolic pressure contour is a function of resistance, compliance, and inertance of an isolated arterial system. The site of measurement therefore is theoretically unimportant, because the system is closed and the pressure is transmitted within the system (Cohn et al. 2004). If this was not the case we might expect to see individuals with SCI have higher arterial compliance due to the much higher use of the arms on a daily basis relative to able-bodied individuals.

The determinants of arterial compliance differ between large and small arteries. This helps explain why differences in the study participants were not seen in large artery compliance (see figure 5) while there was a significant difference in small artery compliance between groups. A power calculation with alpha at 0.05 and power at 0.80 suggests that a sample size of 61 would be required to find significance for large artery compliance between groups. However, it was not expected that large artery compliance would be significantly different between groups based on previous research (Grey et al. 2003) and due to the fact that generally, small artery compliance is considered a better predictor of early cardiovascular disease as it often shows a decrease before, and to a greater degree than large artery compliance (Hypertension Diagnostics 2002). In large
arteries, collagen and elastin are the major determinants of function (Cohn et al. 2004). In smaller arteries and arterioles, NO released from the endothelium plays a significant role in determining calibre and compliance via its actions on smooth muscle (Cohn et al. 2004). Therefore, it follows that a reduced compliance of the small arteries and arterioles is (in part) the result of endothelial dysfunction. However, recent evidence shows that arterial compliance is not necessarily correlated with endothelial function (Westhoff et al. 2007) despite the fact that both arterial compliance (Grey et al. 2003) and endothelial function (De Groot et al. 2005) decrease with cardiovascular disease progression. Results from this study seem to reflect the findings of Westhoff et al. (2007) since no statistically significant differences were found in endothelial function (a very small effect size for FMD (eta squared= 0.00) suggests that the lack of significance was not due to a lack of power) between groups while a difference in small artery compliance was found between groups. Other research (Nair et al. 2005) has shown that vascular compliance as assessed by pulse waveform analysis correlates better with cardiovascular risk factors than does FMD as assessed by high resolution ultrasound. The findings of this study suggest that pulse wave analysis may be a preferred method of cardiovascular health assessment; in addition to supporting the significant difference in small artery compliance seen in other studies, pulse wave analysis is less operator dependent and simpler to use.

12.3. Quality of Life

Studies comparing QOL in individuals with SCI and able-bodied individuals show that SCI groups score significantly lower (Dijkers 2005). However in this investigation, although able-bodied individuals tended to score higher on all questionnaires, no significant differences were found between individuals. Other studies have shown that while those with SCI score significantly lower, differences are not as large as might be expected (Dijkers 2005; Post and Noreau 2005). Indeed,
some literature (Eisenberg and Saltz 1991; Chapin et al. 2004) shows that QOL following SCI covers a wide range of scores from well below to scores that approach or surpass healthy population averages.

It is possible that the subjective nature of most of the questionnaires in this study contributes to the lack of significance and moderate effect sizes for some questionnaires. Indeed, some domains of subjective QOL are found to be equal to or even higher than the general population (Eisenberg and Saltz 1991; Post and Noreau 2005). Subjective QOL questionnaires measure outcomes through the individual’s point of view and results can vary greatly between individuals. In the SCI population there are many potential predictors of subjective QOL including, but not limited to, environmental issues, community reintegration/participation factors such as employment, interpersonal relationships, and social functioning, psychological factors such as loneliness and perceived control on life, health-related factors, injury-related factors, pain and demographics (Boschen et al. 2008). These factors may have had an impact on increasing the variability that was seen in the answers of individuals with SCI in this study.

The large effect size and trend towards significance for physical health and social relationships in the WHOQOL suggests that a larger sample size would show individuals with SCI to be significantly lower in these domains. The trend for lower scores in the social relationship domain of the WHOQOL is owing to two factors: 1) several individuals expressed dissatisfaction with their sex life; indeed the literature shows sexual function is very often impaired due to spinal cord injury (Anderson et al. 2007), and 2) one individual had recently lost their circle of friends as those friendships were centered on a sport in which he can no longer participate. Power analysis using an alpha at 0.05 and a power of 0.80 indicates that we would begin to find statistical significance with an additional 5 participants in each group.
Quality of life has been shown to be enhanced by meaningful relationships; the assumption of responsibility for, and opportunity to exert control over, one's own life; and the ability to engage in personally meaningful occupations (Hammell 2004a). Individuals with lower spinal lesions are more independent than their tetraplegic counterparts. Also, most participants in this study were engaged in personally meaningful occupations and their interest in volunteering for this research study lends itself as evidence of their taking initiative and having control over their own life. Studies of tetraplegics (Bach and McDaniel 1993; Hammell 2004b) have been able to show significant differences in QOL, however participants with spinal injury in these studies number around 15. Our study included half that number of individuals and participants were paraplegic not tetraplegic. Because of this low number and due to the higher function of paraplegics, the non-significant results for questionnaires used in this study are not surprising.

The effect of antidepressant medication on QOL assessments shows that following treatment with medication there is an improvement in social function as measured by tests such as the SF-36 (Kennedy et al. 2001). This further complicates the assessment of psychological measures of quality of life in this study such as the CES-D, SES, and psychological domains within the SF-36 and WHOQOL-BREF. Two individuals with SCI in this study were taking antidepressants when questionnaires were administered. Any improvement which resulted from this medication would presumably decrease the likelihood of finding a significant difference between groups or a larger effect size for questionnaires such as the CES-D.

13. Conclusion

With respect to assessment of QOL, this investigation lends support to other findings. Studies investigating physical function and limitations which result from physical problems show
that the SCI population scores lower compared to able-bodied persons (Leduc and Lepage 2002; Post and Noreau 2005) and in our study the trend for a difference in the physical domain of the WHOQOL supports this well established finding. This study also investigated other measures of emotional QOL assessment such as depression, satisfaction with life, and psychological health as assessed by the WHOQOL and found no trends towards statistical significance. This finding agrees with those of others that show scores of mental health, vitality, and role limitations due to emotional problems and mental health are not lower in SCI than in the general population (Leduc and Lepage 2002; Post and Noreau 2005).

In the assessment of vascular compliance, this study confirms our previous findings (Zbogar et al. 2008), showing that small artery compliance is lower in individuals with SCI. These findings indicate that the assessment of arterial compliance appears to be an important method for the noninvasive, early detection of cardiovascular disease following SCI. This study also supports the finding of Westhoff et al. (2007) who showed that arterial compliance was not correlated with endothelial function and also that perhaps arterial compliance assessment correlates better with cardiovascular risk than does FMD as assessed by ultrasound (Nair et al. 2005).

Investigation of the cardiovascular response to exercise of increasing intensity reflects trends found in other research (Rowell 1986; Gledhill et al. 1994) showing increases in VO$_2$, HR, SV, and Q with increasing exercise intensity. Although statistically significant between group differences were not found in this study, our results yielded trends which have been documented by others (Hopman 1994; Nash et al. 1996; Phillips et al. 1998; Myers et al. 2007) showing that SV is lower in SCI and that HR compensates for this and that able bodied individuals have a higher VO$_2$peak, and Q.

The significant finding yielded by NIRS shows that able bodied and SCI individuals differed in oxygenation of the lower leg. This may be a result of muscle contractions that occur in the leg
musculature as exercise intensity reaches higher levels. Despite being asked to minimize
movement of the legs during the test able bodied participants likely did recruit their legs as
stabilizers to increase leverage with exercise at higher wattages.

Our finding that total haemoglobin in the working muscle continued to increase throughout
the exercise test suggest that blood flow was not a limiting factor in graded exercise using arm
ergometry for both able bodied and SCI individuals. These findings which reflect those of Muraki et
al. (2004) suggest that because the decrease in oxygenated haemoglobin leveled off during
exercise while blood flow increased throughout all stages a limitation to exercise in both able
bodied and SCI groups lies in the muscle. However this study also suggests that individuals with
SCI may, relative to able bodied persons, have a central limitation which is evidenced by a trend
towards lower Q as exercise reached maximal levels. As per the Fick equation, VO₂ is affected by
Q and the lower Q in individuals with SCI results in a lower VO₂ max for individuals with SCI.

14. Limitations

A small sample in this investigation limits the strength of statistical findings in the present
study. Nevertheless, several studies examining exercise response in individuals with SCI have
found statistically and clinically relevant results with sample sizes of 5 to 9 individuals (Hjeltnes
1977; Flandrois et al. 1986; Bhambhani et al. 2000).

The large amount of variability found in cardiovascular responses to exercise could result
from several factors. Most able-bodied participants in this study did not aerobically train using their
upper limbs and many had never used an arm ergometer. Habituation for all participants to this
method of exercise was limited to the 0.5 hours preceding the actual exercise test. While much
habituation is not required for arm cycle ergometry relative to wheelchair ergometry, able bodied
persons still varied greatly in the capability of the arms to reach higher wattages. This variability likely translated into very different values for factors such as SV which exhibited a larger amount of variability than in individuals with SCI across all stages (see table 3).

Measures obtained in this study were determined indirectly. For example resting and exercise SV was indirectly determined via acetylene rebreathing. Moreover, avDO$_2$ was indirectly measured as VO$_2$ divided by Q. However, we anticipate that recruitment would have been more difficult and fewer individuals would have agreed to enroll in the study if measures were direct and therefore invasive.

With respect to potential central and peripheral limitations to exercise, only a handful of factors could be measured in this study: SV, HR, avDO$_2$, total haemoglobin and muscle oxygenation. We are unable to comment on other potential sources of limitation as discussed in section 5.1 or offer, for example, further insight into how factors contributing to SV (e.g. investigation of systolic or diastolic function of the heart which would be afforded by cardiac ultrasonography) respond to exercise and how they differ between individuals with SCI and able bodied controls.

The use of NIRS is restricted to a few cubic centimetres of muscle. We can only speculate on the nature of change in total haemoglobin and oxygenation in other areas of both the working and non-working limb measured in this study. It has been shown that NIRS values can differ significantly within the same muscle (Kennedy et al. 2006) and data from studies on other species indicates that muscle perfusion is far from homogeneous (Piiper and Haab 1991). The absorption spectra of myoglobin and haemoglobin overlap, with myoglobin composing approximately 10% of the signal, and therefore NIRS does not differentiate between these signals in vivo (Boushel, Langberg et al. 2001). Also, quantifying the absolute concentration of any chromophores in the tissue is not possible as the path-length of the light from emitter to detector is unknown and there is
no distinction between absorbed or scattered light. It must be recognized that the measure of total haemoglobin which we took as a measure of blood flow can be influenced not only by increased blood flow, but also by venous obstruction or increased haemoglobin concentration. Also an increase in oxygenated haemoglobin can indicate increased arterial inflow, increased oxygen saturation or an increased concentration of oxygenated haemoglobin (Raisis 2005).

Despite these limitations, NIRS does provide important information regarding trends in muscle oxygenation during exercise and recovery.

Finally, we can only speculate that isometric contraction and leg movement in able bodied individuals contributed to the difference in decline of oxygenated haemoglobin between groups during arm ergometry. The use of EMG would have allowed us to comment more definitively on this issue.
### Table 1a. Participant characteristics (spinal cord injured)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Gender</th>
<th>Age (y)</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>Aerobic Activity (days/week)</th>
<th>TI (y)</th>
<th>Lesion Level</th>
<th>ASIA grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - SCI</td>
<td>M</td>
<td>19</td>
<td>22.6</td>
<td>120</td>
<td>68</td>
<td>3</td>
<td>0.67</td>
<td>T11/12</td>
<td>A</td>
</tr>
<tr>
<td>3 - SCI</td>
<td>M</td>
<td>45</td>
<td>28.4</td>
<td>121</td>
<td>72</td>
<td>6</td>
<td>15</td>
<td>T7/8</td>
<td>A</td>
</tr>
<tr>
<td>4 - SCI</td>
<td>M</td>
<td>31</td>
<td>24.2</td>
<td>117</td>
<td>67</td>
<td>1</td>
<td>11</td>
<td>T6</td>
<td>A</td>
</tr>
<tr>
<td>5 - SCI</td>
<td>F</td>
<td>37</td>
<td>18.6</td>
<td>118</td>
<td>69</td>
<td>2</td>
<td>12</td>
<td>T12</td>
<td>A</td>
</tr>
<tr>
<td>6 - SCI</td>
<td>M</td>
<td>39</td>
<td>24.7</td>
<td>117</td>
<td>66</td>
<td>2</td>
<td>17</td>
<td>T6</td>
<td>A</td>
</tr>
<tr>
<td>7 - SCI</td>
<td>F</td>
<td>33</td>
<td>20.1</td>
<td>138</td>
<td>83</td>
<td>0</td>
<td>29</td>
<td>T5</td>
<td>A</td>
</tr>
<tr>
<td>8 - SCI</td>
<td>M</td>
<td>26</td>
<td>23.7</td>
<td>132</td>
<td>76</td>
<td>1</td>
<td>1</td>
<td>T7</td>
<td>A</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>32.9</td>
<td>23.2</td>
<td>123.1</td>
<td>71.2</td>
<td>2.1</td>
<td>12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>8.6</td>
<td>3.2</td>
<td>8.4</td>
<td>6.0</td>
<td>2.0</td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BMI = body mass index, TI = time since injury, SBP = systolic blood pressure, DBP = diastolic blood pressure, SD = standard deviation**

### Table 1b. Participant characteristics (able bodied)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Gender</th>
<th>Age (y)</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>Aerobic Activity (days/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - AB</td>
<td>M</td>
<td>18</td>
<td>24.0</td>
<td>112</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>3 - AB</td>
<td>M</td>
<td>45</td>
<td>22.1</td>
<td>108</td>
<td>68</td>
<td>4</td>
</tr>
<tr>
<td>4 - AB</td>
<td>M</td>
<td>31</td>
<td>24.6</td>
<td>111</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td>5 - AB</td>
<td>F</td>
<td>42</td>
<td>23.8</td>
<td>116</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>6 - AB</td>
<td>M</td>
<td>39</td>
<td>25.0</td>
<td>102</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td>7 - AB</td>
<td>F</td>
<td>32</td>
<td>20.8</td>
<td>97</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>8 - AB</td>
<td>M</td>
<td>29</td>
<td>25.4</td>
<td>125</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>33.7</td>
<td>23.7</td>
<td>109.9</td>
<td>63.1</td>
<td>2.6</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>9.2</td>
<td>1.6</td>
<td>9.1</td>
<td>5.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**BMI = body mass index, TI = time since injury, SBP = systolic blood pressure, DBP = diastolic blood pressure, SD = standard deviation**
<table>
<thead>
<tr>
<th>Participant</th>
<th>Medications</th>
<th>Dosage</th>
<th>Usage</th>
<th>Possible CV Side Effect</th>
<th>Prevalence of CV Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-SCI</td>
<td>Warfarin</td>
<td>5mg 1x/day</td>
<td>anticoagulant</td>
<td>systemic atheroemboli, cholesterol microemboli</td>
<td>-</td>
</tr>
<tr>
<td>3-SCI</td>
<td>none</td>
<td>-</td>
<td>-</td>
<td>hypotension</td>
<td>rare 3%</td>
</tr>
<tr>
<td>4-SCI</td>
<td>none</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5-SCI</td>
<td>none</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-SCI</td>
<td>Codeine</td>
<td>pm</td>
<td>analgesic</td>
<td>hypotension</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>37.5mg 1x/day</td>
<td>antidepressant</td>
<td>blood pressure</td>
<td>3%</td>
</tr>
<tr>
<td>7-SCI</td>
<td>Gabapentin</td>
<td>400mg 3x/day</td>
<td>neuropathic analgesic</td>
<td>vasodilation, hypertension</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>20mg 1x/day</td>
<td>antidepressant</td>
<td>myocardial infarction, arrhythmias, stroke</td>
<td>0 to 9%</td>
</tr>
<tr>
<td></td>
<td>Baclofen</td>
<td>20mg 4x/day</td>
<td>anti-spasticity</td>
<td>hypotension</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Sennosides</td>
<td>12mg 1x/day</td>
<td>bowel stimulant</td>
<td>none</td>
<td>-</td>
</tr>
</tbody>
</table>

CV= cardiovascular, pm= according to need
Table 3. Descriptive Statistics for aerobic power, HR, SV cardiac output, and a-vDO₂ during the graded exercise test.

### VO₂ (L/min)

<table>
<thead>
<tr>
<th>Stage (% watts)</th>
<th>SCI</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>20</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>40</td>
<td>1.0 ± 0.3</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>60</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>80</td>
<td>1.5 ± 0.4</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>100</td>
<td>1.7 ± 0.4</td>
<td>2.1 ± 0.6</td>
</tr>
</tbody>
</table>

### VO₂ (ml/kg/min)

<table>
<thead>
<tr>
<th>Stage (% watts)</th>
<th>SCI</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.1 ± 0.4</td>
<td>4.4 ± 0.6</td>
</tr>
<tr>
<td>20</td>
<td>10.3 ± 1.3</td>
<td>10.4 ± 1.0</td>
</tr>
<tr>
<td>40</td>
<td>14.2 ± 2.2</td>
<td>14.5 ± 2.8</td>
</tr>
<tr>
<td>60</td>
<td>17.3 ± 2.4</td>
<td>18.4 ± 2.9</td>
</tr>
<tr>
<td>80</td>
<td>20.9 ± 3.1</td>
<td>25.1 ± 6.0</td>
</tr>
<tr>
<td>100</td>
<td>23.7 ± 2.7</td>
<td>28.6 ± 5.7</td>
</tr>
</tbody>
</table>

### HR

<table>
<thead>
<tr>
<th>Stage (% watts)</th>
<th>SCI</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76.9 ± 15.5</td>
<td>71.6 ± 11.7</td>
</tr>
<tr>
<td>20</td>
<td>97.0 ± 18.1</td>
<td>90.7 ± 21.5</td>
</tr>
<tr>
<td>40</td>
<td>116.9 ± 14.1</td>
<td>110.4 ± 23.0</td>
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<tr>
<td>60</td>
<td>148.3 ± 12.3</td>
<td>134.4 ± 19.9</td>
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<tr>
<td>80</td>
<td>165.4 ± 12.6</td>
<td>162.0 ± 17.2</td>
</tr>
<tr>
<td>100</td>
<td>178.0 ± 10.0</td>
<td>171.3 ± 11.4</td>
</tr>
</tbody>
</table>

### SV

<table>
<thead>
<tr>
<th>Stage (% watts)</th>
<th>SCI</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>79.9 ± 22.5</td>
<td>93.6 ± 29.1</td>
</tr>
<tr>
<td>20</td>
<td>81.3 ± 23.0</td>
<td>92.0 ± 36.6</td>
</tr>
<tr>
<td>40</td>
<td>80.9 ± 23.6</td>
<td>96.4 ± 32.6</td>
</tr>
<tr>
<td>60</td>
<td>76.8 ± 20.0</td>
<td>94.4 ± 24.2</td>
</tr>
<tr>
<td>80</td>
<td>80.0 ± 22.7</td>
<td>100.5 ± 30.4</td>
</tr>
<tr>
<td>100</td>
<td>89.1 ± 20.5</td>
<td>105.2 ± 32.0</td>
</tr>
</tbody>
</table>

### Q

<table>
<thead>
<tr>
<th>Stage (% watts)</th>
<th>SCI</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.0 ± 1.4</td>
<td>6.4 ± 1.3</td>
</tr>
<tr>
<td>20</td>
<td>7.7 ± 2.1</td>
<td>7.8 ± 1.8</td>
</tr>
<tr>
<td>40</td>
<td>9.3 ± 2.3</td>
<td>10.2 ± 2.3</td>
</tr>
<tr>
<td>60</td>
<td>11.2 ± 2.3</td>
<td>12.5 ± 2.4</td>
</tr>
<tr>
<td>80</td>
<td>13.0 ± 3.0</td>
<td>16.3 ± 5.5</td>
</tr>
<tr>
<td>100</td>
<td>15.8 ± 3.4</td>
<td>18.0 ± 5.7</td>
</tr>
</tbody>
</table>

### a-vDO₂ (ml/L)

<table>
<thead>
<tr>
<th>Stage (% watts)</th>
<th>SCI</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>51.1 ± 11.4</td>
<td>50.0 ± 4.9</td>
</tr>
<tr>
<td>20</td>
<td>101.9 ± 33.1</td>
<td>99.8 ± 17.8</td>
</tr>
<tr>
<td>40</td>
<td>113.6 ± 26.8</td>
<td>104.3 ± 13.8</td>
</tr>
<tr>
<td>60</td>
<td>112.1 ± 22.0</td>
<td>107.8 ± 6.0</td>
</tr>
<tr>
<td>80</td>
<td>116.7 ± 19.5</td>
<td>113.8 ± 15.7</td>
</tr>
<tr>
<td>100</td>
<td>108.4 ± 14.1</td>
<td>117.5 ± 11.3</td>
</tr>
</tbody>
</table>

VO₂= aerobic power, HR= heart rate, SV= stroke volume, Q= cardiac output, a-vDO₂= arteriovenous oxygen difference, SCI= individual with spinal cord injury, AB= able-bodied individual. Values are means ± SD.
Table 4. Descriptive statistics for arterial compliance in individuals with SCI and able-bodied individuals

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>F</th>
<th>Sig.</th>
<th>eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Artery Compliance</td>
<td>SCI</td>
<td>6.91</td>
<td>3.70</td>
<td>5.46</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>10.51</td>
<td>1.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Artery Compliance</td>
<td>SCI</td>
<td>19.59</td>
<td>6.74</td>
<td>0.86</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>23.93</td>
<td>10.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Descriptive statistics for endothelial function in individuals with SCI and able-bodied individuals

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>F</th>
<th>Sig.</th>
<th>eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD%</td>
<td>SCI</td>
<td>6.84</td>
<td>4.31</td>
<td>0.00</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>6.82</td>
<td>3.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMD%</td>
<td>SCI</td>
<td>22.74</td>
<td>9.65</td>
<td>0.22</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>24.66</td>
<td>4.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMD/NMD ratio</td>
<td>SCI</td>
<td>0.91</td>
<td>0.08</td>
<td>0.75</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>0.88</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FMD= flow mediated dilatation, NMD= nitroglycerine mediated dilatation
Figure 1. Atherosclerosis timeline

Taken from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 104)
Figure 2a-f. Cardiovascular and aerobic responses to incremental exercise test

2a
Aerobic Power

2b
Aerobic Power

2c
Heart Rate

2d
Stroke Volume

2e
Cardiac Output

2f
Arteriovenous Oxygen Difference

mean±SD; * significantly different from previous stage (p < 0.05)
Figure 3a-d. Muscle total haemoglobin and oxygenation response to incremental exercise test.

<table>
<thead>
<tr>
<th>Arm Total Hb</th>
<th>Leg Total Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watts (%)</td>
<td>Watts (%)</td>
</tr>
<tr>
<td>0 20 40 60 80 100</td>
<td>0 20 40 60 80 100</td>
</tr>
</tbody>
</table>

Figure 3a: Arm O2Hb

Figure 3b: Leg O2Hb

Figure 3c: Arm O2Hb

Figure 3d: Leg O2Hb

mean±SD; * significantly different from 0% watts (p < 0.05); † significantly different from able-bodied individuals (p < 0.05)
Figure 4. Small artery compliance

![Graph showing small artery compliance](image1)

Figure 5. Large artery compliance

![Graph showing large artery compliance](image2)
15. References


16. Appendices

Appendix A1:

Satisfaction with Life Scale (SWLS)

The following five statements are very broad and require you to think about your life in general without reference to any particular area of your life. The questions pertain to how you feel about your life right now. You may agree or disagree with each of the five statements by placing a number between 1 and 7 on the line beside each statement. Please be open and honest in your responding and use the following scale to guide your responses.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Slightly Disagree</td>
<td>Slightly Agree</td>
<td>Agree</td>
<td>Strongly Agree</td>
<td></td>
</tr>
</tbody>
</table>

_____ 1. In most ways my life is close to my ideal.

_____ 2. The conditions of my life are excellent.

_____ 3. I am satisfied with my life.

_____ 4. So far I have gotten the important things I want in life.

_____ 5. If I could live my life over, I would change almost nothing.
Appendix A2.

Rosenberg Self-Esteem Scale

The scale is a ten item Likert scale with items answered on a four point scale - from strongly agree to strongly disagree. The original sample for which the scale was developed consisted of 5,024 High School Juniors and Seniors from 10 randomly selected schools in New York State.

Instructions: Below is a list of statements dealing with your general feelings about yourself. If you strongly agree, circle SA. If you agree with the statement, circle A. If you disagree, circle D. If you strongly disagree, circle SD.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>On the whole, I am satisfied with myself.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>2.*</td>
<td>At times, I think I am no good at all.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>3.</td>
<td>I feel that I have a number of good qualities.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>4.</td>
<td>I am able to do things as well as most other people.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>5.*</td>
<td>I feel I do not have much to be proud of.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>6.*</td>
<td>I certainly feel useless at times.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>7.</td>
<td>I feel that I'm a person of worth, at least on an equal plane with others.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>8.*</td>
<td>I wish I could have more respect for myself.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>9.*</td>
<td>All in all, I am inclined to feel that I am a failure.</td>
<td>SA</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>I take a positive attitude toward myself.</td>
<td>SA</td>
<td>A</td>
</tr>
</tbody>
</table>
Appendix A3:

**CES-D Scale**

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

**During the past week:**

<table>
<thead>
<tr>
<th>1.</th>
<th>I was bothered by things that usually don't bother me.</th>
<th>1</th>
<th>Rarely or None of the Time (Less than 1 day)</th>
<th>2</th>
<th>Some or Little of the Time (1-2 days)</th>
<th>3</th>
<th>Occasionally or a Moderate Amount of Time (3-4 days)</th>
<th>4</th>
<th>Most or All of the Time (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>I did not feel like eating; my appetite was poor.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>3.</td>
<td>I felt that I could not shake off the blues even with help from my family or friends.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>4.</td>
<td>I felt that I was just as good as other people.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>5.</td>
<td>I had trouble keeping my mind on what I was doing.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>6.</td>
<td>I felt depressed</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>7.</td>
<td>I felt that everything I did was an effort.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>8.</td>
<td>I felt hopeful about the future</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>9.</td>
<td>I thought my life had been a failure.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>10.</td>
<td>I felt fearful.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>11.</td>
<td>My sleep was restless.</td>
<td>1</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>2</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>3</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>4</td>
<td>Most or All of the Time (5-7 days)</td>
</tr>
<tr>
<td>Question</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I was happy.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I talked less than usual.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I felt lonely.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. People were unfriendly.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I enjoyed life.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I had crying spells.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. I felt sad.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. I felt that people dislike me.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. I could not get &quot;going&quot;.</td>
<td>Rarely or None of the Time (Less than 1 day)</td>
<td>Some or Little of the Time (1-2 days)</td>
<td>Occasionally or a Moderate Amount of Time (3-4 days)</td>
<td>Most or All of the Time (5-7 days)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Appendix A4:

**Quality of Life Questionnaire (SF-36)**

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>Very Good</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much better than a year ago</td>
<td>Somewhat better than a year ago</td>
<td>About the same as a year ago</td>
<td>Somewhat worse than a year ago</td>
<td>Much worse than a year ago</td>
</tr>
</tbody>
</table>

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes, limited a lot</td>
<td>yes, limited a little</td>
<td>No, not limited at all</td>
</tr>
</tbody>
</table>

   a. vigorous activities (e.g., running, lifting heavy objects, participating in strenuous sports)
   
   b. moderate activities (e.g., moving a table, pushing a vacuum cleaner, bowling, playing golf)
   
   c. lifting or carrying groceries
   
   d. climbing several flights of stairs
   
   e. climbing one flight of stairs
   
   f. bending, kneeling, or stooping
   
   g. walking more than a mile
   
   h. walking several blocks
   
   i. walking one block
   
   j. bathing or dressing yourself
4. During the past 4 weeks, have you had any of the following problems with your work or other daily activities as a result of your physical health?

a. cut down the amount of time you spent on work or other activities
   Yes  No
b. accomplished less than you would like
   Yes  No
c. were limited in the kind of work or other activities
   Yes  No
d. had difficulty performing the work or other activities (e.g., it took extra effort)
   Yes  No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. cut down the amount of time you spent on work or other activities
   Yes  No
b. accomplished less than you would like
   Yes  No
c. didn't do work or other activities as carefully as usual
   Yes  No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with friends, family, neighbors, or groups?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Slightly</td>
<td>Moderately</td>
<td>Quite a Bit</td>
<td>Extremely</td>
</tr>
</tbody>
</table>

7. How much bodily pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Very Mild</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>Slightly</td>
<td>Moderately</td>
<td>Quite a Bit</td>
<td>Extremely</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the time</td>
<td>Most of the time</td>
<td>A good bit of the time</td>
<td>Some of the time</td>
<td>A little of the time</td>
<td>None of the time</td>
</tr>
</tbody>
</table>

a. Did you feel full of pep?_________

b. Have you been a very nervous person?_______

c. Have you felt so down in the dumps that nothing could cheer you up?___________

d. Have you felt calm and peaceful?________

e. Did you have a lot of energy?________

f. Have you felt downhearted and blue?________

g. Did you feel worn out?____________

h. Have you been a happy person?____________

i. Did you feel tired?________

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the time</td>
<td>Most of the time</td>
<td>Some of the time</td>
<td>A little of the time</td>
<td>None of the time</td>
</tr>
</tbody>
</table>

11. How True or False is each of the following statements for you?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely True</td>
<td>Mostly True</td>
<td>Do Not Know</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly False</td>
<td>Definitely False</td>
</tr>
</tbody>
</table>

a. I seem to get sick a little easier than other people_____ 

b. I am as healthy as anybody I know__________ 

c. I expect my health to get worse_______ 

d. My health is excellent_______
Appendix A5:

The World Health Organization Quality of Life (WHOQOL) – BREF

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. Please choose the answer that appears most appropriate. If you are unsure about which response to give to a question, the first response you think of is often the best one. Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life in the last four weeks.

<table>
<thead>
<tr>
<th></th>
<th>Very poor</th>
<th>Poor</th>
<th>Neither poor nor good</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td>3</td>
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<td>4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following questions ask about how much you have experienced certain things in the last four weeks.
<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>A moderate amount</th>
<th>Very much</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>How well are you able to concentrate?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>How safe do you feel in your daily life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>How healthy is your physical environment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

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<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Mostly</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Do you have enough energy for everyday life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Are you able to accept your bodily appearance?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>Have you enough money to meet your needs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>How available to you is the information that you need in your day-to-day life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>To what extent do you have the opportunity for leisure activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Very poor</th>
<th>Poor</th>
<th>Neither poor nor good</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>How well are you able to get around?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>How satisfied are you with your sleep?</td>
<td>Very dissatisfied</td>
<td>Dissatisfied</td>
<td>Neither satisfied nor dissatisfied</td>
<td>Satisfied</td>
</tr>
<tr>
<td>---</td>
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<td>------------------</td>
<td>-------------</td>
<td>----------------------------------</td>
<td>-----------</td>
</tr>
<tr>
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<td></td>
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<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with your ability to perform your daily living activities?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with your ability for work?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td></td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with yourself?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td></td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with your personal relationships?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
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<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with your sex life?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
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<td>4</td>
<td>5</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with the support you get from your friends?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
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<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with the conditions of your living place?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with your access to health services?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td></td>
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<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>How satisfied are you with your transport?</th>
<th>Very dissatisfied</th>
<th>Dissatisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

The following question refers to how often you have felt or experienced certain things in the last four weeks.

<table>
<thead>
<tr>
<th></th>
<th>How often do you have negative feelings such as blue mood, despair, anxiety, depression?</th>
<th>Never</th>
<th>Seldom</th>
<th>Quite often</th>
<th>Very often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td></td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Do you have any comments about the assessment?
Appendix B:

Physical Activity Questionnaire

Name: ____________________

The following questions ask you about your involvement in physical activity and how you feel about your physical fitness. Please choose the answer that appears most appropriate for you.

1. Frequency
   a. Over a typical week how many times do you engage in aerobic activity that is sufficiently prolonged and intense to cause sweating and a rapid heart beat?
      0 1 2 3 4 5 6 7
   b. Over a typical week how many times do you engage in strength training activities?
      0 1 2 3 4 5 6 7

2. Intensity
   When you engage in physical activity, what effort do you think that you make?
   very light light moderate intense very intense
   1 2 3 4 5

3. Perceived Fitness
   In a general sense, how would you rate your current physical fitness?
   very poor poor average good very good
   1 2 3 4 5
Appendix C:

ASIA: Standard neurological classification of spinal cord injury
Appendix D:

**Modified Borg Scale**

<table>
<thead>
<tr>
<th>SCALE</th>
<th>SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Effort At All</td>
</tr>
<tr>
<td>0.5</td>
<td>Very Very Slight (Just Noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very Slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Some What Severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very Severe</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very Very Severe (Almost Maximum)</td>
</tr>
<tr>
<td>10</td>
<td>Maximum</td>
</tr>
</tbody>
</table>