Spinal Cord Injury and Cardiovascular Health:

Effect of Arm Crank Exercise at Aerobic High and Moderate Intensity

- A pilot study.

Master Thesis in Clinical Health Science,

Obesity and Health

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Abstract

Background: Cardiovascular disease (CVD) is now the leading cause of death in individuals with spinal cord injury (SCI). The SCI population is among the least physically active in society. Physical activity is known to reduce risk factors for CVD. The role of intensity of aerobic arm exercise in individuals with a chronic SCI is not fully investigated. **Purpose:** To compare the effects from aerobic high intensity interval training (HIT) (85% - 95% of peak heart rate (HR_{peak})) and isocaloric aerobic continuous moderate exercise (CME) (70% of HR_{peak}) on peak oxygen uptake (VO_{2peak}), waist circumference (WC) and endothelial function measured as flow-mediated dilatation (FMD) in the brachial artery. **Methods:** 10 individuals with SCI paraplegia were randomized to HIT or CME arm crank exercise three times a week for eight weeks. **Results:** No significant differences in VO_{2peak} between the groups from baseline to post-test were found. However, there was a favorable trend towards a higher increase in VO_{2peak} in the HIT group compared to the CME group, 28.1±7.5 ml· kg^{-1}·min^{-1} - 31.2±8.8 ml· kg^{-1}·min^{-1} versus 24.6±6.9 ml· kg^{-1}·min^{-1}- 23.8±5.4 ml· kg^{-1}·min^{-1}, respectively, (P= 0.051). No difference in FMD or WC within or between the groups from baseline to post-test was found. **Conclusions:** The findings from the present pilot study showed no significant difference between high- and moderate intensity arm crank exercise in terms of VO_{2peak}, waist circumference or flow-mediated dilatation. However, there was a favorable trend towards a higher increase in VO_{2peak} from arm crank exercise at aerobic high intensity compared to isocaloric exercise at moderate intensity. Exercise at aerobic high intensity was feasible for the individuals with SCI paraplegia in this study. Future randomized studies with larger sample sizes to confirm our findings are needed.

Relevance:

Evidence based practice is essential to assure the best possible quality of rehabilitation medicine, and in this case, for the cardiovascular health of individuals with SCI paraplegia. The findings from the present study may be incorporated into daily treatment routines, and will contribute with new knowledge in the development of exercise guidelines for the SCI population.

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1.1 Introduction

A spinal cord injury (SCI) leads to impairments of motor, sensory and autonomic functions below the level of injury [1]. The degree and type of impairment depend upon the severity and level of the injury [2].

Survival after SCI has increased dramatically the last decades [3], mainly due to improvements in medical treatment [4, 5]. The increased life expectancy is primarily attributed to increased survival the first two post-injury years [6]; improvement in survival past the first two years are small and not significantly different [6]. Historically, causes of death in persons with SCI have been related to lung- and renal complications [5]. These are now exceeded by cardiovascular disease (CVD), which is the most common cause of death among persons with SCI, as well as the able-bodied population [5, 7]. In chronic SCI, prevalence of CVD is significantly higher, occurs at an earlier age [8], and the death rates are higher compared to able-bodied [5, 9]. Virtually all risk factors for CVD are more prevalent among persons with SCI [5, 10]. The SCI population is among the least physically active in society [11, 12], and is, consequently, generally deconditioned [13]. Physical inactivity is a major, independent risk factor for CVD and premature death in able-bodied [14-16]. In the SCI population, physical activity has been found to reduce the risk of developing CVD and its comorbidities; such as type II diabetes, hypertension and obesity [2, 9] thus reducing the risk of premature death [15]. The most commonly used exercise modalities among persons with SCI are arm crank ergometers, wheelchair ergometers, hand bikes and hybrid machines; which combine arm cycling with passive leg movements [11]. The equipment is expensive, and in Norway, it is granted from the social welfare system only for those below the age of 26. Furthermore, limited opportunities to perform physical activity, and a sedate life style, are also factors that may explain the inactive life style in this population [13].

Aerobic capacity is, together with smoking, the strongest predictor of death among both healthy persons and patients with cardiovascular disease [17-19]. There is an inverse relationship between aerobic capacity and death [19]. In the able-bodied population, aerobic high intensity exercise (HIT) is found to be more effective for increasing aerobic capacity and reducing cardiovascular risk factors compared to aerobic continuous moderate exercise (CME) [20-26]. To our knowledge, this has not been extensively assessed in the SCI population, and no specific consort statement exercise guidelines are available for this group [27].

To our knowledge, only two studies have compared the effect from arm aerobic exercise with different training intensities on aerobic capacity and cardiovascular risk factors in the SCI population [1, 28]. The findings from these studies are inconclusive in terms of which is most effective in improving $VO_{2peak,}$ thus more research is needed. Furthermore, no studies have, to our knowledge, assessed the effect from HIT and CME arm exercise on endothelial function and WC in individuals with SCI. Therefore, the primary aim of the present study was to compare the effect from isocaloric aerobic high- and moderate intensity arm crank exercise on peak oxygen uptake in spinal cord injured persons with paraplegia. The secondary aims were to compare the effect on endothelial function and waist circumference, and to assess the feasibility of aerobic exercise at high intensity in individuals with SCI paraplegia.

Our primary hypothesis was that aerobic high intensity exercise (85%-95% of HR_{peak}) three times a week for eight weeks increased VO_{2peak} more than isocaloric aerobic continuous moderate exercise (70% of HR_{peak}) performed three times a week for eight weeks.

Secondary, we hypothesized that aerobic exercise at high intensity improved endothelial function and waist circumference more than isocaloric moderate aerobic exercise.

1.2 Theoretical background

1.2.1 Spinal cord injury

The spinal cord is the connection between the brain and the body, where motor and sensory information travels [2, 29]. An SCI leads to loss of motor, sensory and autonomic functions below the level of injury [1]. An SCI is divided into paraplegia and tetraplegia, depending on the level of injury. Paraplegia is defined as loss or impairment of motor and/or sensory function in the thoracic (Th), lumbar (L) or sacral (S) parts of the spinal cord. There is normal function in the upper extremities, but the trunk, lower extremities and the pelvis are affected, depending on the level of injury. Injury to the cauda equina and conus medullaris are included, but injury to nerves distal to the neural canal is not [29]. Tetraplegia defines an injury at the cervical (c) level, which results in loss or impairment of function in the upper extremities, as well as the trunk, lower extremities and the pelvis [29]. Depending on the degree of partial preservation below the level of injury, and the preservation of function in the lowest sacral segments, SCI is classified as complete or incomplete [29, 30] Furthermore, SCI is divided into traumatic and non-traumatic injuries, based on the etiology [31]. The most frequent causes of a traumatic injury are falls and traffic accidents [32]. Non-traumatic injuries may be caused by inflammation, tumors, ischemic causes, myelitis, spina bifida, among more [33].

Incidence of SCI worldwide is reported to lie between 10.4 and 83 per million inhabitants per year [34]. In Norway, the average annual incidence of traumatic SCI is 21.2 per million [35]; approximately 108 new causes each year. The incidence of non-traumatic SCI in Norway is estimated to be about the same as traumatic injuries [36], but these numbers are less known, due to heterogeneous causes, and lack of standardized methods of registration [33].

1.2.2 Life expectancy after spinal cord injury

Life expectancy for individuals with SCI has increased dramatically due to advances in medical treatment [3-5]. Improvements in survival are mainly related to the two first post-injury years; from 1973 to 2004, mortality in this period was reduced by 40% [6]. However, improvements in survival rates beyond these first two years after injury are not statistically significant [6]. Persons with an incomplete SCI have the same life expectancy as able-bodied [37], whereas those with complete injuries still have reduced life expectancy [7, 37-39]. However, the difference in mortality is far smaller than earlier decades [39].

Historically, the most common causes of death among individuals with SCI have been respiratory- and renal complications. These still remain common causes of death, but are now exceeded by CVD [5]. The longer a person lives with an SCI, the more the diseases and cause of death resemble the able-bodied population, independent of degree of completeness of the injury [7]. These persons are therefore exposed to the same life-style related diseases as able-bodied [3-5, 13]. Individuals with SCI have higher mortality rates from both symptomatic and asymptomatic CVD, and death occurs at an earlier age compared to able-bodied. This is more pronounced in long-term SCI [5, 9]. The risk of developing CVD is proportional to the level and extent of injury and age [4, 16, 40]. In persons with SCI tetraplegia, CVD may be undetected, because of the interruption of pain perception, and because persons with SCI more seldom exert themselves to a level that evokes symptoms of CVD [5]. Several of the factors that cause a shortened life expectancy, are potentially treatable factors, such as diabetes, heart disease, smoking and reduced pulmonary function [37]. There is higher prevalence of virtually all risk factors for CVD in the SCI population [5, 41].

1.2.3 Physical inactivity

Physical inactivity is a major, independent risk factor for CVD and premature death in able-bodied [14-16]. Physical activity performed on a regular basis, and high aerobic capacity is associated with reduced risk of premature death and CVD, and there is a dose-response relationship; the highest levels of physical activity are associated with the lowest risk of premature death [9, 15, 19]. The SCI population is among the least physically active in society [11]; one study found that 50% of the participants reported to perform no leisure time physical activity (LTPA) at all [12]. Those with a complete tetraplegia, [5, 42] and those with long-time SCI are found to have the lowest levels of regular physical activity [12]. The majority of persons with SCI are deconditioned, due to a sedate lifestyle and limited opportunities to engage in physical activity [13]. Special equipment is usually necessary when performing upper body exercise. This equipment is expensive and, in Norway, is usually not granted by the social welfare system for those above the age of 26. This limits the possibilities to perform physical activity. Many persons with SCI develop inactivity-related chronic diseases, such as cardiovascular disease and type II diabetes [11]. The low level of physical activity is likely to explain, at least in part, why persons with an SCI have an increased risk of CVD [16, 27], which increase the risk of developing secondary complications [27, 43]. Activities of daily life are not adequate to maintain a sufficient level of cardiovascular fitness

[9]. Therefore, persons with SCI need to perform regular, structured physical activity to reduce the risk of secondary complications and to improve their aerobic capacity [2].

1.2.4 Aerobic capacity and exercise

Maximal oxygen uptake (VO_{2max}) is the maximum rate of oxygen measured during ramped exercise, and is an important determinant of maximal aerobic capacity, i.e. a determinant of endurance capacity during prolonged sub-maximal exercise [19, 44]. This is the gold standard measure of maximal aerobic capacity and depends of the integrated health and effort of the lungs, cardiovascular system, and skeletal musculature [19]. The main determinants of aerobic capacity are $VO_{2max,}$ work economy, and lactate threshold [44-46]. VO_{2max} is the product of cardiac output (CO) and arterio-venous oxygen difference (a-$vO_{2\ diff}$) at physical exhaustion [19, 44] and is described using the Fick'e equation: (HRxSV) x (avO_{2diff}) [19, 47, 48]. CO is the result of heart rate (HR) x stroke volume (SV) and accounts for the supply part of the oxygen transport [19] A-vO_{2diff} describes the amount of oxygen extracted from the skeletal musculature, and is the difference in oxygen content between arterial and venous blood, which accounts for the demand part of the oxygen transport. Both supply and demand may limit oxygen uptake [49]. In healthy able-bodied persons performing whole-body exercise, VO_{2max} is primarily limited by supply, whereas in untrained and several patient groups the limitation is in the demand part of the oxygen transport [44, 50-52]. The criteria for obtaining a true VO_{2max} is that the individual reaches and sustains a plateau in VO_{2max}, i.e. and increase in ventilation without an increase in VO_{2max}, and is usually applied on healthy individuals [19]. The term VO_{2peak} is used when a plateau is not reached [51, 53]. This is the case when the maximal test is limited by local muscular factors, and not by central factors; a so-called "demand" limitation [53] After SCI, both the supply and demand will be affected [54]. In work with smaller muscle groups, as arm crank exercise, demand plays a more important role, and is the limiting factor, rather than supply [44, 54]. Maximal aerobic capacity is affected by level of physical activity, age [19, 55], sex, and the presence of disease and medications [19]. There is 8% to 10% expected decrease in aerobic capacity for each decade in nonathletic persons. Also in those who engage in physical activity on a regular basis, a decrease in aerobic capacity is seen, but to a smaller degree [56]. Oxygen uptake is 10% to 20% greater in men compared to women [55]. In SCI, the level and extent of injury influence VO_{2peak}, and training effect measured as increased $VO_{2\ peak}$ is inversely proportional to level of injury, and degree of completeness [57, 58].

Upper-body exercise is usually performed using arm crank ergometers (Figure 1), wheelchair ergometers, hand bikes or hybrid machines, which combine arm cycling with passive leg movements [11]. Upper body exercise is found to significantly increase VO_{2peak} in paraplegic spinal cord injured [59], and paraplegics who engage in physical activity on a regular basis have a higher VO_{2peak} compared to their inactive counterparts [60-62]. They do, however, not reach the level of VO_{2peak} of able-bodied [2, 63]. In the HUNT-study from 2011,VO_{2peak} was assessed on 4631 healthy able-bodied adults with mean age 48 years. They found overall mean VO_{2peak} 40.0 ±9.5 ml· kg^{-1} · min^{-1} [17]. VO_{2peak} tested on a wheelchair ergometer in 166 adults, mean age 33.1±11.9 years with SCI paraplegia Th6-10, was 24.7±10.1 ml· kg^{-1} · $min^{-}1$. In men with SCI tetraplegia C4-8, mean age 34.5±12.1 years, mean VO_{2peak} was 12.6±6.6 ml· kg^{-1} · min^{-1} [64].

Aerobic capacity is, together with smoking, the strongest predictor on death among both healthy, able-bodied and patients with cardiovascular disease [17, 56]. There is an inverse relationship between aerobic capacity and death. The strongest health benefits are found by increasing the level of physical activity among the least fit [19]. These benefits are more associated with recent than distant activity [65]. In the able-bodied, healthy population, guidelines for physical exercise exist [66, 67]. There is currently no consort statement forming exercise guidelines for the SCI population. Most studies that examine the effects of exercise on physical fitness in people with SCI are of low quality [27, 68]. The role of intensity in increasing VO_{2peak} in individuals with SCI has not been fully investigated

1.2.5 Limitations to aerobic capacity after SCI

In most cases, an SCI leads to a reduction in muscle strength, endurance and motor control in the lower extremities to such a degree, that effective whole-body exercise is not achievable. Thus, exercise is performed by the use of the upper extremities [2]. Compared to whole-body exercise, upper-body exercise involves less active muscle mass, which limits maximal performance, and limits the possibilities to achieve a high aerobic capacity [69, 70]. Improving aerobic capacity is more challenging when performing upper-body exercise, because muscle fatigue is often reached before the intended training intensity is achieved [9]. Maximal aerobic capacity with the upper extremities usually reaches only 70% of the maximal whole-body exercise capacity [71].

The sympathetic nervous system (SNS) is completely or partially absent below the level of SCI, which attenuates exercise performance. Level and severity of the SCI correlates with

autonomic dysfunction [72]. During aerobic exercise, cardiovascular responses are crucial in order to meet the increased metabolic demands of the active muscles. In able-bodied, there is redistribution of blood from non-active tissues, which supplies the working muscles, and increases CO through an increase in SV and HR. These responses are attributable to the actions of the SNS [69, 73]. These are impaired after SCI; impaired sympathetic activity leads to lack of vasoconstriction of the blood vessels below the level of injury [69]. In SCI above T6, redistribution of blood from the splanchnic area is also impaired [74]. Together with the absence of the skeletal muscle-venous pump [69], this leads to pooling of blood in the pelvic area, causing reduced redistribution of blood to the working muscles, and reduced end-diastolic left-ventricular (LV) filling [13, 69], which leads to reduced stroke volume [75]. In individuals with cervical and high thoracic SCI, there are lower maximum heart rates and impaired blood pressure responses during incremental aerobic exercise [72, 76]. This is most pronounced in injuries at and above thoracic level1[2]. Heart rate responses similar to those in able-bodied are seen in injuries below the level of Th5 [72]. At the same intensity, cardiac output is similar, in spite of a lower stroke volume. This is compensated for by a higher heart rate [63, 69, 77].

Figure 1, arm crank exercise. (Picture used with permission).

1.2.6 Endothelial function

The endothelium is a single layer of cells covering all blood vessels in the body [78], which senses and responds to internal and external stimuli [79]. The capacity of the blood vessels to respond to physical and chemical stimuli gives a possibility to self-regulate tonus and adjust blood flow and distribution of blood to the different parts of the body [8, 79]. An increased blood flow leads to shear stress, and many blood vessels respond to shear stress by dilating. This response is called flow mediated dilatation (FMD) [79]. The mechanism behind the dilatation response is that shear stress stimulates to the release of nitric oxide (NO), which in

turn leads to relaxation of the smooth muscle, and consequently, dilatation of the blood vessel [78-82]. NO is of particular interest, because the reduction of bioavailability of NO might play an important role in the pathogenesis of vascular disease, as it is an antiatherogenetic molecule [78]. Endothelial dysfunction is considered an important factor in the development of atherosclerosis, hypertension and heart failure [79]. FMD is a valuable tool, because it reflects the risk of developing cardiovascular disease [8]. The assessment is non-invasive, and thus puts a smaller burden on the patient and is less time consuming than invasive assessments [83]. In the presence of cardiovascular disease, the endothelium loses its regulatory function [8]. A low FMD response is associated with increased risk of cardiovascular disease, and cardiac events [78], atherosclerosis, hypertension and heart failure [79]. Normal FMD response indicates low risk of cardiac event [84].

Inactivity and age negatively affect endothelial function and NO- availability [81, 85, 86]. Regular physical activity enhances FMD in the brachial artery in able-bodied persons [87] with a variety of diagnoses, such as diabetes type 2 [88], Polycystic ovarian syndrome [89], and elevated blood pressure [90]. HIT is shown to be more effective in improving endothelial function than CME, in lean adolescents [91]. The possible mechanism is that physical activity increases blood flow, which increase the capability of the endothelium to release nitric oxide and therefore may restore endothelial function [87]. This can partly explain why physical exercise reduces the risk of developing cardiovascular disease [86].

1.2.7 Waist circumference

Obesity is a common secondary complication following SCI [42]. Body weight often gradually increases after as SCI, especially after the first post-injury year [43]. As a consequence of SCI, total daily energy expenditure decreases due to loss of muscle mass [42], and reduced physical activity levels [12, 42]. Loss of muscle mass reduces fat free mass (FFM), which is the most crucial predictor of resting metabolic rate (RMR) [92], which is in turn the main contributor of daily energy expenditure [42]. RMR is found to be 14% - 27% lower in persons with SCI compared to able-bodied [42]. Obesity is a major risk factor for several CVD risk factors [93-95], and causes medical problems and reduces quality of life [96]. Visceral adipose tissue has been found to be most strongly associated with CVD [93].

Body mass index (BMI) is a commonly used measure of body fat, and is calculated using the following formula: weight (kg) / height (m^2) [95]. BMI is found to be an insensitive measure of obesity in SCI-injured persons, and is an inconsistent marker on risk of CVD [94, 97].

Body weight comprises lean tissue, fat tissue and bone mass [98]. Since these factors are altered after SCI, adiposity may not be identified using BMI. Persons with chronic SCI have greater fat mass and less fat-free mass per unit BMI compared to able-bodied, showing that BMI underestimates body fat in persons with SCI [98]. Waist circumference (WC) is a simple and inexpensive way to assess abdominal obesity [94]. It has not been validated as an indirect measure of visceral adipose tissue, but it has been found to be a more precise measurement of visceral adipose tissue than BMI, and a strong relationship between WC and risk factors for coronary heart disease (CHD) exist [97, 99-101]. Abdominal obesity is defined as a WC greater than 102 cm in men and 88 cm in women [102]. The common complications of obesity are more closely related to the distribution of body fat than to the absolute degree of fatness per se [101]. WC is influenced by physical activity in able-bodied and individuals with SCI, and a lower WC is found in those who are physically active compared to their inactive counterparts [103, 104].

2. Methods

Participants were recruited from The Department of Spinal cord injuries, at St. Olavs Hospital, Trondheim University Hospital, Norway. All tests and training were performed at St. Olavs Hospital, Norway. Data collection started in August 2013, and was completed in October 2013. Written and oral informed consent was obtained from each participant before inclusion. The study was approved by the Regional Committees for Medical and Health Research Ethics, and conducted in accordance with the Declaration of Helsinki [105] .

2.1 Study design

Randomized clinical trial, in a pre-post design.

2.2 Variables

Independent variable in this study is exercise intensity. Dependent variables are $VO_{2peak,}$ waist circumference, body weight, and endothelial function. Primary end point is $VO_{2peak.}$

2.3 Participants

Adult men and women with a spinal cord injury were recruited.

2.3.1 Inclusion criteria

Paraplegia (Th2 or lower), traumatic spinal cord injury, spina bifida and myelitis, time since injury >1 year.

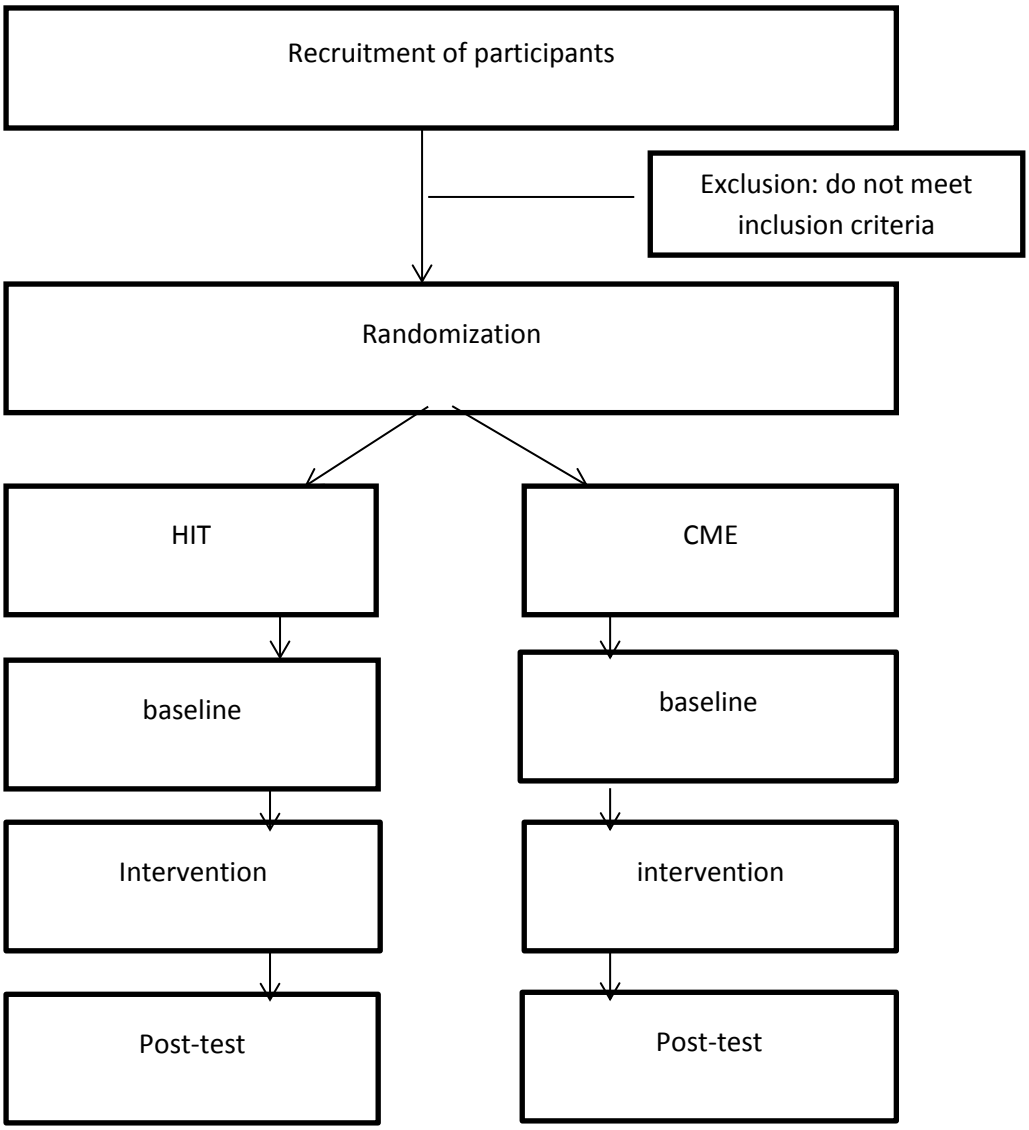
2.3.2.Exclusion criteria

Tetraplegia (Th 1 or higher), non-traumatic injury (except from spina bifida and myelitis), cardiovascular disease, diabetes mellitus type I, pregnancy, decubitus, cancer, and time since injury (TSI) < 1 year.

2.4 Randomization procedure

After stratified by age (50 years), the participants were randomized into aerobic high intensity interval training (HIT) or isocaloric aerobic continuous moderate exercise (CME). A flow chart of the process is described in Figure 2. Randomization was performed by a computer program by the Unit for Applied Clinical Research, NTNU, Norway.

Figure 2, flow chart of the randomization- and intervention process.



HIT: aerobic high interval training, CME: aerobic continuous moderate exercise.

2.5 Training protocols

Both groups performed arm crank exercise with Monark Rehab trainer 881 (Monark exercise AB, Vansbo, Sweden), three times a week for eight weeks under the supervision of a nurse or a physiotherapist. HIT consisted of 10 minutes warm up at 70% of peak heart rate (HR_{peak}), followed by four bouts of four minutes intervals at 85% - 95% of HR_{peak}. The intervals were interspersed by a three minutes active break arm cranking at approximately 70% of HR_{peak}. The session was completed by a three minutes cool-down period at 70% of HR_{peak}. CME was performed at 70% of HR_{peak}. To make the two interventions isocaloric, each CME session had duration of 50 minutes. This was calculated based on mean VO_{2peak} in the HIT group at baseline. Participants in the HIT group consumed on average 373.35 kcal per training session.

This equals 49.78 minutes ≈ 50 minutes per session continuous exercise at 70% of HR_{peak} in the CME group. A compliance of 80% of the total of exercise sessions was set as criteria for completing the study. Participants completing the program were eligible for analyses. All participants kept a training diary. The HIT group registered the following after each training session: mean heart rate in the last 15 seconds of each interval, and date. The participants in the CME group registered: heart rate at 20 minutes, 30 minutes and 47 minutes, and date. Heart rate was monitored continuously during exercise, to assure that the exercise was performed at the intended intensity.

2.6 Measurements

All tests were performed pre- and post-intervention.

2.6.1 Peak oxygen uptake

A portable Metamax II Cortex ergospirometry system (Cortex Biophysik GmbH, Leipzig, Germany) was used to measure VO_{2peak} and Metasoft 1.11 was used for analysis. Oxygen and carbon dioxide exchange, ambient air and pressure are measured. The oxygen uptake measured by the Metamax II is on average 4% higher than that of the Douglas bag technique [106].

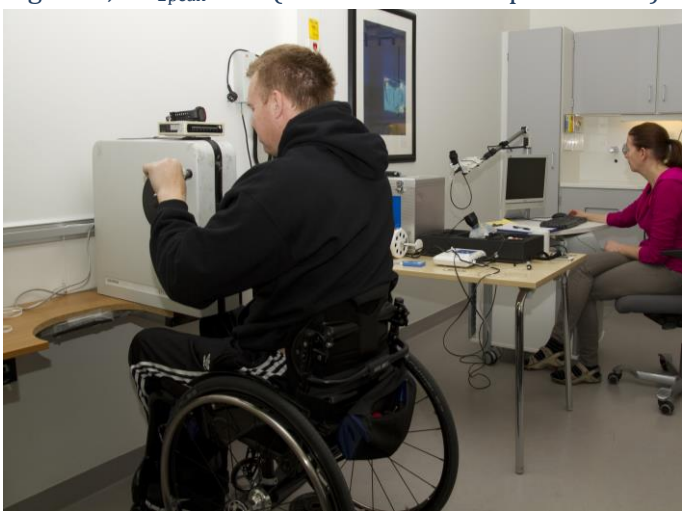
Calibration included calibration of the volume transducer by using a 3-L standardized calibration syringe and barometric pressure (Hans Rudolp Jager, GmbH, Germany), and calibration of gas concentration with ambient air and chemically standardized two-point calibration gas (15% O_2 and 5% CO_2). This was completed prior to testing, and not more than five tests were performed before a new calibration was done.

The test was performed with an arm-crank ergometer (Ergomed 840L, Siemens. CAmed medical systems GmbH, Köln, Germany). (Figure 3). This ergometer was modified for arm-crank exercise by changing the pedals for arm use. It is equipped with an electrical brake system, which ensures that the watt indicated on the screen is the actual power the participants produce. Before the test was executed, the arm-crank ergometer was calibrated by bringing the ergometer to 90 repetitions per minute (RPM). A braking force was applied, and we ensured that the time required to decline to a given RPM was correct (35 RPM in 40 seconds with a 0 watt braking load, and 0 RPM in 18 seconds with a 25 Watt braking load (Siemens Ergo Med Operation Manual, 1985).

The participants were instructed to refrain from coffee and tobacco in the morning before the test and to refrain from exercise 24 hours prior to the test. The participants were informed about the test procedure, and were instructed to perform to their maximal limit.

We used a ramp protocol [107], adjusted to last between 6-12 minutes [108]. After 10 minutes of warm up, the participants were instructed to arm crank exercise at a steady pace at 70 repetitions per minute (RPM). Work rate increments were increased by 10-20 watt (W) per minute until volitional fatigue. Verbal encouragements were given during exercise testing, especially towards the end of the test to help the participants reach their maximal capacity. VO_{2peak} was measured as the average of the highest measurements over 30 seconds. Criteria for reaching VO_{2peak} was a respiratory exchange ratio (R)> 1.05, blood lactate > 7 mmol and Borg scale >15.

Figure 3, VO_{2peak} test. (Picture used with permission)



2.6.1.1.Blood lactate concentration

Blood lactate concentration was measured by the hemolytic blood sample taken from the participant's fingertip immediately after ending the VO_{2peak} test with the portable Lactate Pro Analyzer LT-1710.

2.6.1.2 Heart frequency

Heart frequency was registered every minute during the test with Polar ® Accurex watches (Polar Electro, Oy, Finland). The accuracy of measurement of heart frequency with Polar ® Accurex is ± 1 heart beat (Polar electro, Finland, 1997). HR_{max} was measured as the highest recorded heart rate at the end of the VO_{2peak} test, plus 5 beats.

2.6.1.3 Body weight

Body weight in kilograms (kg) was measured using a Seca 959 digital chair scale (Hamburg, Germany). Prior to testing, the scale was calibrated according to 90/384 CEE directive, III class calibration.

2.6.1.4 Subjective rating of perceived exertion

Subjective rating of perceived exertion (RPE) was assessed immediately after the VO_{2peak} test, using the Borg 6-20 scale [109].

2.6.2 Endothelial function

Endothelial function of the brachial artery was measured by flow mediated dilatation (FMD), with high soluble vascular ultrasound (12- MHz ultrasound probe, Vivid 7 System, GE Vingmed Ultrasound, Horten, Norway). The participants were instructed to refrain from exercise 48 hours prior to the test, and were asked to fast, and refrain from coffee, smoking and snuff the same morning. The test was performed with the participants in supine resting position, in a quiet room with stable temperature. The left brachial artery was examined above the antecubital fossa. Blood flow was estimated by pulsed Doppler velocity. Baseline was measured at rest before an occlusion was made. A cuff was placed at the distal part of the forearm [79]. Occlusion was made by inflating the cuff to 250 mmHg for 5 minutes, and then deflated, thus creating a high-flow state in the artery. All images were measured at baseline and continuously at three minutes following cuff deflation. FMD response is expressed as the percentage increase in the artery's peak post-deflation diameter from baseline average diameter [80, 110]. All ultrasound images were analyzed in random order using EchoPACtm (GE Vingmed Ultrasound AS). Diameter was measured from intima to intima using calipers with 0, 1 - mm resolution.

2.6.3 Waist circumference

Waist circumference was measured used a non-elastic, flexible measuring tape at the level of the umbilicus after normal expiration. The participants were sitting in an upright position in their personal wheelchair.

2.7 Statistical analyses

Based on the small sample size, and because assumptions of normally distributed data were not met, non-parametric tests were used for analyses. Mann-Whitney Test was used to assess differences between AIT and CME group between baseline and post- test. To assess differences within the groups between from baseline and post-test, the Wilcoxon Signed Ranks Test was used. Statistical significance was set at $P < 0.05$. Data are presented as mean ± standard deviation (SD). Mean and SD are chosen instead of medians, to make our data comparable to other studies. Statistical analyses were performed using SPSS® Statistics 20 computer software (SPSS Inc. Chicago, IL, USA).

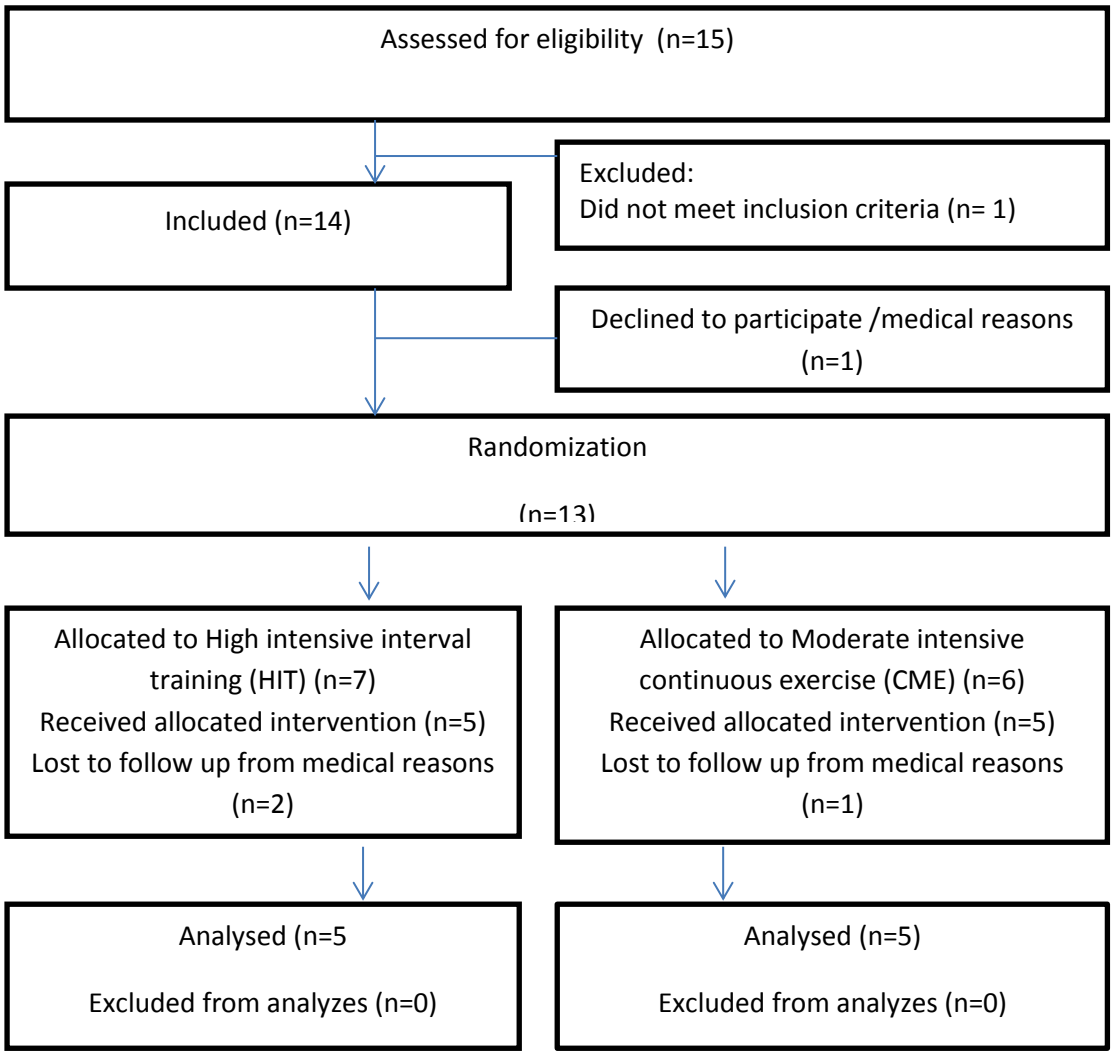
2.8 Ethical considerations

All testing and training was supervised by an experienced nurse, physiotherapist or physiologist. A health assessment was performed prior to training in order to identify risk factors for cardiovascular events. All participants were approved for training by a medical doctor specialized in the rehabilitation medicine and SCI medicine prior to the exercise intervention. No adverse effects were expected form the intervention, as aerobic exercise at high and moderate intensity have been shown to be safe [111].

3. Results

Eligible participants were recruited from June 2013 to August 2013 at St.Olavs Hospital. 15 persons were recruited into this study. One person was excluded because inclusion criteria were not met, and another withdrew before randomization was performed, due to medical reasons. Therefore, 13 persons were randomized into HIT or CME. Two persons withdrew before testing and training started, due to medical reasons, and one person withdrew during the intervention period from medical reasons not related to the intervention. 10 persons completed the intervention, and 96.7 % of the training interventions were completed in the group as a whole, (Figure 4).

Figure 4, flow chart.



3.1 Participant characteristics

Participant characteristics are presented in Table 1.

Level of physical activity prior to the intervention period was assessed by using a self-report questionnaire, LTPAQ-SCI [112], where the participants reported minutes of mild, moderate and heavy intensity performed in their leisure time over the seven previous days. According to the answers, the participants were untrained or moderately trained. One of the 10 participants reported to have performed activities at high intensity the last seven days, and two participants reported to exclusively have performed activities of mild intensity. The majority of the participants (7/10) reported to have performed activities of moderate or mild and moderate intensity.

There were no significant differences in age, time since injury and antropometry between the groups at baseline.

Table 1. Participant characteristic.

Variables	**HIT** **n=5**	**MCE** **n=5**	***P*-value**
Age (years)	45.8 ± 6.3	42.8 ± 14.3	1.00
Time since injury (years)	15.2 ± 13.5	15.0 ± 11.3	0.75
Level of injury	Th4, Th8, Th8, Th9,Th11	Th4, Th8, Th8, Th12, L2	
Height (cm)	175.4 ± 8.5	186.0 ± 6.4	0.09
Gender (male/female)	4/1	5/0	

Data are presented as mean ±standard deviation. HIT: aerobic high intensity interval training, CME: aerobic continuous moderate exercise.

3.2 Aerobic capacity

There were no significant differences in VO_{2peak} between the groups at baseline. In the CME group, one of the participants underwent a life style change parallel to the intervention. This included a self-reported strict diet and high doses of exercise at moderate intensity, which exceeded our recommendations for exercise in the intervention period. Therefore, this person is excluded from data analyses of VO_{2peak} and WC. There were no significant differences between baseline and post-test in VO_{2peak} between or within the groups. VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) increased by 11.3±10.9 % in the HIT group, and was reduced by 2.0±7.1% in the CME group (P=0.051). VO_{2peak} (l/min) increased by 8.4 ±10.8% in the HIT group from baseline to

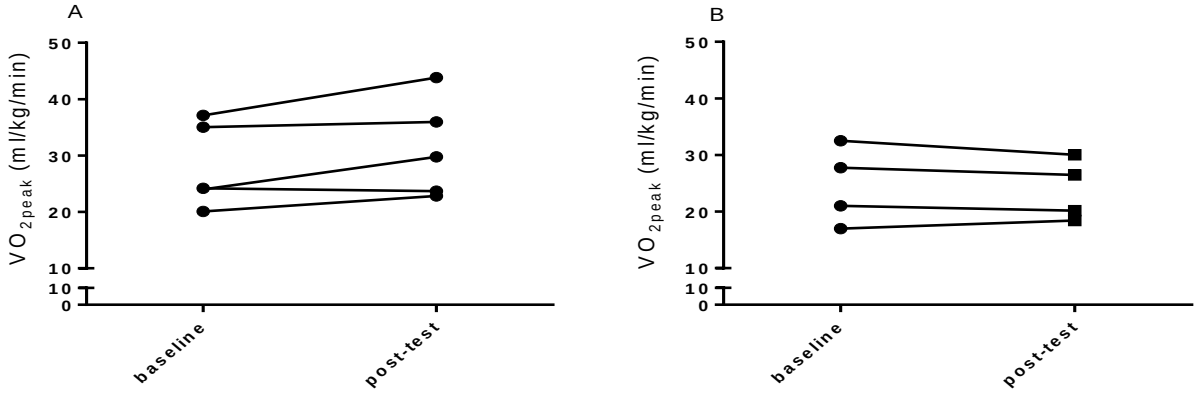
post-test. In the CME group, there was a 2.6±7.8 % reduction, (*P*=0.051). (Table 2). Individual differences in VO_{2peak} are presented in Figure 5.

Table 2. Peak aerobic capacity; baseline and post-test.

Variables	**HIT baseline n= 5**	**HIT Post-test n=5=**	**CME baseline n=4**	**CME Post-test n=4**	***P*-value between groups baseline-post-test**	***P*-value HIT baseline-post-test**	***P*-value CME baseline-post-test**
$VO_{2peak,}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	28.1±7.5	31.2±8.8	24.6±6.9	23.8±5.4	0.051	0.08	0.47
VO_{2peak} , ($L \cdot min^{-1}$)	2.14±0.56	2.33±0.70	2.27±0.68	2.19±0.57	0.051	0.23	0.27
Total pulmonary ventilation ($L \cdot min^{-1}$)	86.85±24.50	96.7±28.57	79.52±30.71	83.86±30.84	0.35	0.14	0.72
Respiratory exhange ratio	1.18±0.08	1.18±0.03	1.15±0.08	1.14±0.01	0.91	0.89	0.72
Lactate (mmol/l)	11.40±1.63	11.46±3.64	9.83±1.71	9.60±1.62	1,00	0.85	0.47
Watt	111.0±20.7	142.0±34.9	107.5±41.9	120.0±50.3	0.26	0.04	0.26
Borg scale	17.8±0.5	18.8±1.3	17.8±1.0	18.3±1.1	0.80	0.10	0.16
Peak heart rate (bpm)	169.2±9.6	172.0±5.4	174.8±21.4	171.0±23.7	0.11	0.27	0.11
Weight, kg	77.0±11.4	75.1±11.9	94.8±24.5	94.0±23.3	0.46	0.07	1.00

Data are presented as mean ±standard deviation. HIT: aerobic high intensity interval training, CME: aerobic continuous moderate exercise.

Figure 5. VO_{2peak} at baseline and post-test. Individual values.

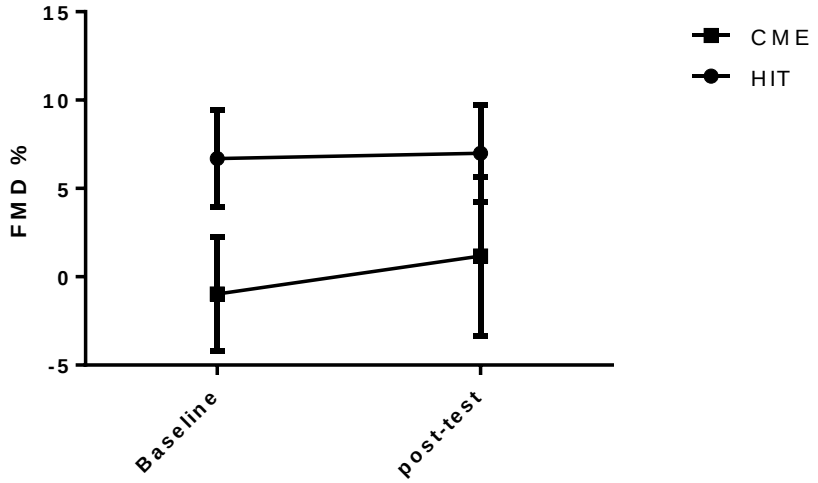


A: aerobic high intensity interval training, B: aerobic continuous moderate exercise.

3.3 Endothelial function

The present study included one female participant. According to current guidelines, the phase of the subject's menstrual cycle should be registered, as it may influence FMD [113]. This was not registered in our study, and therefore, this participant is excluded from analyses on FMD. At baseline, FMD was significantly higher in the HIT group compared to the CME group (P=0.014). There were no significant differences between baseline and post-test between or within the groups, and no significant differences between the groups at post-test (P=0.142),(Figure 6). FMD for the whole group was 2.4±4.9% at baseline and 3.8±6.0% at post-test.

Figure 6. Flow mediated dilatation, baseline and post-test.

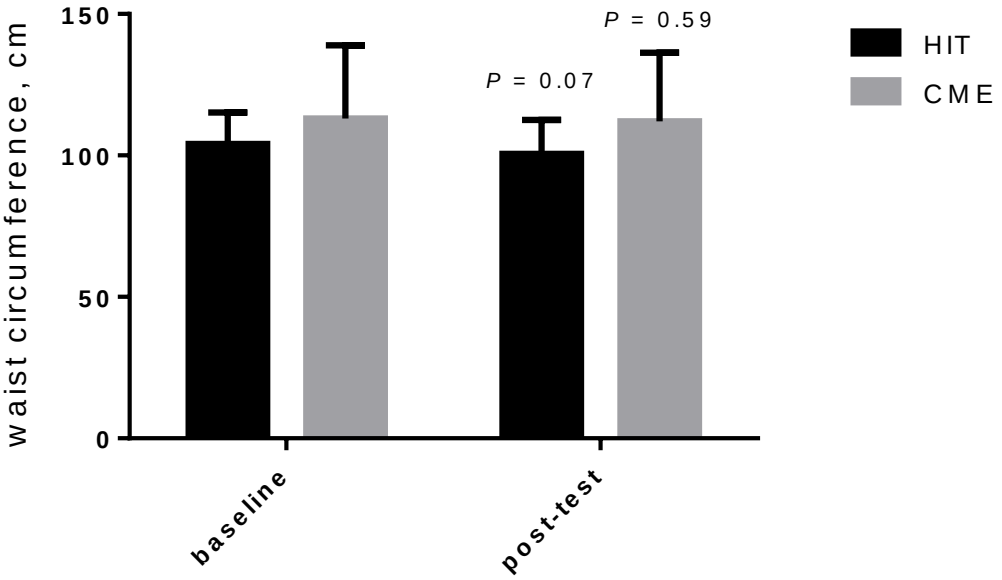


HIT: aerobic high intensity interval training, CME: aerobic continuous moderate exercise.

3.4 waist circumference

No significant differences within or between the groups from baseline to post-test were found in WC. WC was reduced by 3.5±2.5 cm in the HIT group, and by 1.0±4.5 cm in the CME group (*P*= 0.39), (Figure 7). At baseline, WC was 108.0±18.4 cm in the group as a whole, 104.0±11.2 in HIT and 113.0±26.0 in CME.

Figure 7. waist circumfence, baseline and post-test.



HIT: aerobic high intensity interval training, CME: aerobic continuous moderate exercise.

4. Discussion

The current pilot study did not reveal a significant difference in VO_{2peak}, WC or endothelial function in the brachial artery from baseline to post-test between or within the HIT and CME groups. This is in contrast to our primary hypothesis.

4.1 Peak oxygen uptake

Although not significant, there was a favorable trend towards a higher increase in VO_{2peak} from baseline to post-test in the HIT group compared to the CME group (Figure 4). There was a significant increase in Watt between baseline and post-test in the HIT group, but no significant differences were found in the CME group. This indicates that HIT may be more effective in terms of improving VO_{2peak} compared to CME.

In the CME group, there was a reduction in VO_{2peak} between baseline and post-test. One explanation could be that the intervention consisted of smaller volumes of exercise than the participants usually would perform, since they were instructed not to exercise at high intensities during the intervention period. This is not likely, however, since only one of the participants of the CME group reported to have performed exercise at high intensity prior to the study. Although not significant, HR_{peak}, R and lactate decreased from baseline to post-test in the CME group (Table 2). This may indicate that the participants in the CME group did not exert themselves to the same degree at post-test, resulting in a decrease in VO_{2peak}. Another explanation is that the measured reduction in VO_{2peak} is within the measurements errors of the equipment. As a qualitative observations in the HIT group, one of the participants had a decrease in VO_{2peak} between baseline and post-test (Figure 4). The training diary shows that this person was in the lower part of the prescribed intensity zones of 85% - 95% of HR_{peak} through the majority of the intervals. Moholdt et al found that percentage of HR_{max} within the high-intensity zone significantly effects the increase in VO_{2peak}, where those exercising at >92% of HR_{max} improved VO_{2peak} more than those exercise at 88-92% and <88% of HR_{max} [114]. This may explain the lack of improvements in VO_{2peak} for this person.

There was a significant increase in Watt between baseline and post-test in the HIT group, but no increase was seen in the CME group. This supports the trend toward a higher increase in VO_{2peak} in the HIT group.

Two other studies have compared the effects from different intensities during arm exercise on VO_{2peak} in individuals with SCI, with conflicting results. De Groot et al. compared the effects from aerobic exercise at high- (70% - 80% of heart rate reserve (HRR)) to low- (40% - 50%

of HRR) intensity on six recently injured persons three times a week for eight weeks. They found a significantly higher increase in VO_{2peak} for the group as a whole, and significantly higher improvements in the high intensity group compared to the low intensity group. This is in contrast to the findings in the present study, and to the study of Hooker et al., where the effect from aerobic wheelchair ergometry at high- (70% - 80% of HRR) and moderate- (50% - 60% of HRR) intensity for 20 minutes, three times a week for eight weeks was compared. They did not find significant improvements in VO_{2peak} in either of the groups [28]. However, caution must be taken when comparing these studies due to methodological diversities in terms of level of injury of the participants, years since injury, intensity, and testing procedures of VO_{2peak}. In both studies, participants with SCI paraplegia and tetraplegia were mixed together, and both studies were executed with small sample sizes. Also, the interventions compared are not isocaloric. De Groot et al. found a significant increase in VO_{2peak} in the whole group. The participants in this study were recently injured [1]. In the acute stage, spontaneous recovery is expected [115, 116]. Therefore, some of the improvements may be related to spontaneous recovery, and not solely from the exercise intervention.

Studies on able-bodied adults have concluded that HIT has superior effects compared to CME in increasing VO_{2max} and reducing risk factors for diabetes and CVD [117] in persons with coronary artery disease [26], and heart failure [21]. The favorable trends towards higher increases in VO_{2peak} in the HIT group in the present study indicate that these results also may apply to individuals with SCI.

4.2 Endothelial function

No significant changes in FMD were found between or within the groups between baseline and post-test.

Our results are in line with two studies of Thijssen et al. [118, 119], who found no significant changes in FMD in the brachial artery after four and six weeks of hybrid training. This is in contrast to studies in the able-bodied population, where whole-body physical activity has been shown to improve endothelial function [87] These improvements are believed to be attributable to repetitive increases in local stress on the endothelium [82]. A possible explanation to the lack of significant difference in FMD between baseline and post-test may be related to an impaired blood flow, due to reduced redistribution of blood to the active

muscles in the arm during exercise [69]. Thus, the local stress on the endothelium during arm crank exercise may not be sufficient to impose changes in endothelial function.

The participants in the present study and in the studies of Thijssen et al. [118, 119] use a manual wheelchair for transporting themselves, and thus use their upper extremities to a large degree in their daily life. This is the case even for those who do not exercise on a regular basis. Therefore, based on the fact that endothelial adaption is considered to be based on local rather than systemic processes the initial training status of the arms might be high, which limits the effect from the intervention [119]. However, FMD values in the present study are lower compared to those found in the able-bodied adult population. Mean relative FMD in brachial artery for all participants in the present study was 2.4±4.9% at baseline and 3.8±6.0% at post-test. In the HUNT-study, overall mean FMD in 4739 healthy adults, mean age 53 years, was 4.9 ±4.2% [120]. De Groot et al. also found lower FMD response in the brachial artery in individuals with SCI compared to able-bodied controls [121]. There is higher prevalence of virtually all risk factors for CVD in the SCI population [5, 41]. FMD relates to cardiovascular risk [84, 110], and a low FMD response is associated with increased risk of cardiovascular disease, and cardiac events [78]. Therefore, a low FMD may be explained by the high prevalence of CVD risk factors in the SCI population, in spite of the high levels of physical activity of the arm. In the present study, risk factors for CVD were present; with abdominal obesity (mean WC 108.0 ±18.4 cm), and a lower VO_{2peak} : 28.1±7.5 ml· kg^{-1} · min^{-1} in HIT and 24.6±6.9 ml· kg^{-1} · min^{-1} in CME at baseline, vs. 40.0 ±9.5 ml· kg^{-1} · min^{-1} in able-bodied in the HUNT-study [17].

4.3 Waist circumference

There were no significant differences in WC between baseline and post-test within or between the groups.

To our knowledge, no studies have assessed the effect of different exercises on WC in individuals with SCI. Rosety-Rodriguez et al. studied the effect from 12 weeks of arm cranking exercise of moderate intensity (50-65% HRR) 3 times a week on 17 persons with complete SCI with level of injury ≤ Th5 [122]. In contrast to the present study, they did find a significant reduction in WC from baseline to post-test. This study differs from the present study in terms of a) they assessed the effect from exercise at moderate intensity only, b) a longer duration program (12 weeks vs. 8 weeks) and c) larger sample size. Previous studies have suggested that higher improvements in VO_{2peak} are found in studies with longer

interventions periods [123]. It is likely that this also applies to changes in WC, and that the significant reduction found in the study of Rosety-Rodriguez et al. might be due to the longer intervention. Also, sample size is larger (17 vs. 10 participants), which gives stronger evidence, thus a smaller reduction from baseline to post-test in needed to reach significant changes.

The intervention in the present study consisted of exercise only, with no dietary intervention. Studies on able-bodied have concluded that exercise without diet interventions in not an effective weight loss therapy in able-bodied adults who are overweight and obese [124], and this may explain the absence of significant reductions in WC.

5. Study limitations

This study is conducted with small a sample size, and heterogeneous groups, which obviously affect the statistical power, thus makes it difficult to generalize our findings. Recruitment of participants with an SCI is challenging, based on the low prevalence of SCI. In addition, in the present study the participants needed to be residents in the Trondheim area.

More accurate measures might have been achieved by the use of more reliable measurement methods, in terms of control of intensity during exercise, abdominal obesity, and physical activity levels prior to the intervention. To have more control of intensity during training, data from the heart rate monitor would preferably be transferred to a computer after completing each session, where the exact heart rate during each exercise sessions can be read. Due to technical problems with the watches, this was not done. More advanced methods in assessing adiposity and visceral adipose tissue would have given us more sensitive measurements. These are, however, more time- and cost consuming, and were therefore not achievable in the present study. Also, there are many activity monitors available at the marked. As an alternative to the LTSA-SCI, wrist bands monitors could have given us valuable information about the physical activity levels of the participants prior to the intervention.

6. Conclusions

In the current pilot study no significant differences in VO_{2peak}, FMD or WC between baseline and post-test between the HIT and CME groups were found. There was, however, a trend towards a higher increase in VO_{2peak} in the HIT group compared to the CME group. This is the first study that assesses the effect from aerobic exercise at high and moderate intensity on WC

and FMD in brachial artery in individuals with SCI paraplegia. The present study showed that HIT is feasible for individuals with SCI paraplegia. All participants were able to execute the training intervention, and all participants in the HIT group reached their high intensity zones.

Future studies with larger and more homogeneous groups assessing the effect of different intensities during aerobic exercise in individuals with SCI are needed. This can be accomplished through randomized multi center studies.

Abbreviations

CVD= cardiovascular disease

SCI = spinal cord injury

HIT= high intensity interval training

MCE= moderate continuous exercise

HR_{peak} = maximal heart rate

VO_{2peak} = peak oxygen uptake

WC = Waist circumference

FMD= Flow mediated dilatation

C = cervical

Th= Thoracic

L = Lumbar

LTPA = leisure time physical activity

HRR = Heart rate reserve

VO_{2max} = maximal oxygen uptake

CO= cardiac output

$a\text{-}vO_{2\ diff}$ = arteriovenous oxygen difference

SNS = sympathetic nervous system

HR = heart rate

SV = stroke volume

LV= left ventricular

NO= nitric oxide

FES= functional electrical stimulation

FFM = fat free mass

RMR = resting metabolic rate

BMI = body mass index

CHD = coronary heart disease

SD= standard deviation

Kg: kilograms

RPE = rating of perceived exertion

Bl = baseline

Post = post-test

La =Blood lactate concentration

mmol/L = millimoles per liter

V'E =Total pulmonary ventilation

R= respiratory exchange ratio

Borg = Borgs scale

Bpm = beats per minute

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