Development of non-exercise prediction equations for peak oxygen consumption in individuals with spinal cord injury using seismocardiography

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June 1st, 2021 - Master's Thesis - 10th Semester- Sports Science

Resumé

Lavt konditionsniveau er en prædiktor for hjerte-kredsløbssygdomme. Rygmarvsskadede-individer er en gruppe med særlig lavt konditionsniveau, og høj dødelighed som følge af hjerte-kredsløbssygdomme. En metode til at måle konditionsniveau, er ved en maksimal iltoptagelsestest. Denne test er dog dyr, besværlig og ubehagelig at udføre, især for individer med rygmarvsskade. Konditionsniveau kan i stedet estimeres ved brug af specifikke konditions-ligninger, hvor fysisk arbejde ikke udføres. Disse konditions-ligninger er dog mindre præcise. Konditions-ligningerne indeholder typisk variabler såsom; højde, vægt, alder og køn. En sådan konditions-ligning er befolknings-specifik, men der findes ingen konditions-ligning for individer med rygmarvsskade. For at have klinisk relevans er det vigtigt, at konditions-ligningerne er relative præcise i deres estimering. Seismokardiografi har vist sig, at forbedre præcisionen af en konditions-ligning udviklet på rørige individer. Seismokardiografi er en ny metode, som måler hjertets-bevægelser ved hjælp af et accelerometer.

Dette kandidatspeciale havde til formål at udvikle en konditions-ligning, for individer med rygmarvsskade. I udviklingen af konditions-ligningen indgik mål, som kan tages ved et årligt helbredstjek, samt seismokardiografi. Målene blev taget ved en indledende test, hvor forsøgspersonernes maksimale iltoptagelse ligeledes blev målt. Målene fra den maksimale iltoptagelsestest, blev brugt til udvikling af konditions-ligningen.
16 individer med rygmarvsskade blev herefter inddelt i to grupper; en kontrolgruppe og en træningsgruppe, med otte individer i hver gruppe. Kontrolgruppen levede som de plejede i seks uger. Træningsgruppen gennemgik seks ugers kørestols-modificeret ro-træning, indeholdende tre træninger af 30 minutter om ugen.
Efter seks uger, blev de udviklede ligninger (fra indledende test), afprøvet på målinger fra opfølgende test. Dette var for at se, om konditions-ligningerne kunne forudse ændringer i konditionsniveau. Desuden undersøgte vi sammenhængen mellem ændringerne i de målte helbreds- og seismokadiografi variabler, og ændringerne i det målte konditionsniveau.

Vi udviklede syv mulige konditions-ligninger til individer med rygmarvsskade. Alle syv konditions-ligninger var mere præcise end konditions-ligninger udviklet på rørige individer (benyttet på individer med rygmarvsskade). De syv udviklede konditions-ligninger viste sig, at kunne forudsige konditionsniveau efter seks uger. Dog var de mest komplekse af konditions-ligningerne mindre præcise efter seks uger. Der var en sammenhæng mellem ændringer i syv seismokardiografi mål og ændringer af konditionsniveau. Der var dog ingen af de ændrede seismokardiografi mål, der indgik i de syv konditions-ligninger.

Syv ligninger blev udviklet til, at prædiktere konditionsniveau for individer med rygmarvsskade. Alle syv modeller viste sig bedre, end allerede udviklede modeller på rørige individer. Vi anbefaler, at de syv udviklede ligninger valideres inden benyttelse i klinisk sammenhæng. Fremtidige studier bør undersøge de seismokardiografi parametre, der ændrede sig i sammenhæng med individernes konditionsniveau, til brug i fremtidige kondition-ligninger.

Abstract

Objective
Low cardiorespiratory fitness (CRF) is a known predictor for cardiovascular disease (CVD). Individuals with spinal cord injury (SCI) have low CRF, and increased risk for CVD, with CVD being the leading cause of mortality. The American Heart Association recommends CRF to be estimated at least once a year, at least by use of a non-exercise prediction equation (NEPE). NEPEs typically rely on measures such as; age, sex and body mass index. However, no NEPE exists for individuals with SCI. A recent study has explored seismocardiography (SCG) to improve the predictive power of NEPEs among able bodied individuals (AB) (AB-NEPE). Using clinical measurements normally obtained at yearly health checks, in combination with SCG, ***part one*** of this study aims to develop a SCI specific NEPE (SCI-NEPE) to estimate peak oxygen consumption (VO_{2peak}), and compare it to commonly used AB-NEPE. ***Part two*** will evaluate if a SCI-NEPE can predict changes in VO_{2peak} following a six week training intervention. Additionally, we will explore associations between changes in outcome variables and VO_{2peak} in response to training.
Method
In ***part one*** 18 participants (males=11; age=49.6±8.7 yrs) with SCI were included. Clinical and SCG measurements were collected at baseline (BL). Stepwise multiple forward/backward linear regression, was used to develop multiple SCI-NEPEs, and the developed SCI-NEPEs were compared to commonly used AB-NEPEs. For ***part two***,16 participants were allocated into two groups; control (n=8) or training (n=8). The training intervention consisted of 30 minutes moderate-to-heavy wheelchair modified rowing exercise, performed three times a week for six weeks. Clinical- and SCG measurements were collected at six week follow-up (6W), and were fed into the SCI-NEPEs, to evaluate how well SCI-NEPE could predict training induced changes in VO_{2peak}. Furthermore, changes in clinical- and SCG measurements were correlated with changes in VO_{2peak}.
Results
In ***part one***, seven NEPEs for SCI were developed (SCI-NEPE-M1-M7), where SCI-NEPE-M7 demonstrated the highest correlation (R) and lowest standard error of estimate (SEE) (R=.992; SEE=.968mL·kg^{-1}·min^{-1}; p<.01). In ***part two***, SCI-NEPE-M3 had a R=.787; SEE=4.0mL·kg^{-1}·min^{-1}, where SCI-NEPE-M5 could predict the direction of change by 57%. Seven changes in SCG measurements correlated with changes in VO_{2peak} (p<.05).
Conclusion
In ***part one***, based on the high R and low SEE, SCI-NEPE-M7 vastly outperformed all commonly used AB-NEPEs. In ***part two***, the predictive accuracy for all SCI-NEPEs fell at 6W compared to BL, but still vastly outperformed all compared AB-NEPEs in both R and SEE. Our results indicate that the more complex SCI-NEPEs were possibly prone to overfitting, and they all need to be validated before being used in a clinical setting. Changes

in seven SCG measurements (not included in the developed SCI-NEPEs), were found to correlate with changes in VO_{2peak} and warrants further investigation.

Introduction

Research from the past 30 years, clearly shows that low cardiorespiratory fitness (CRF) is a predictor of cardiovascular disease (CVD) and all-cause mortality (Ross et al., 2016). CVD is the leading cause of mortality in individuals with spinal cord injury (SCI) (Garshick et al., 2005), with a prevalence of asymptomatic and symptomatic CVD of 25 - 50%, versus 5 - 10% in able-bodied individuals (AB) (Myers et al., 2007). Worldwide there are between 250,000 and 500,000 individuals with SCI, with 15 - 40 new cases per million per year (Sekhon and Fehlings, 2001; WHO, 2021). In Denmark, approximately 3,000 individuals have a SCI, with 130 - 160 new cases annually (Møller-Nielsen et al., 2010). Individuals with SCI have heightened risk factors for CVD, including high cholesterol, high percentage of adipose tissue, and a higher incidence rate of diabetes, compared to healthy individuals (Bauman et al., 1999; Demirel et al., 2001; Lee et al., 2005; Phillips et al., 1998; Yekutiel et al., 1989). One of the major contributors to these risk factors and low CRF, in the SCI population, is a sedentary lifestyle caused by loss of motor function in the locomotive apparatus (Jacobs and Nash, 2004; Myers et al., 2007). CRF is important for activities of daily living in individuals with SCI, as limited physical ability makes it difficult to perform daily activities, and a high CRF thereby contributes to enhanced physical independence (Janssen et al., 1994; Sisto and Evans, 2014). American Heart Association recommends CRF to be assessed at least once a year, during routine clinical visits, to better monitor and guide individuals at risk (Balady Gary J. et al., 2010; Peterman et al., 2020, 2019; Ross et al., 2016).

A direct measure of CRF is maximum oxygen consumption (VO_{2max}) (Ross et al., 2016). The gold standard for measuring VO_{2max} is graded exercise testing till exhaustion with concurrent measurement of respiratory gas exchange (GET-RGE) (Bentley et al., 2007; Ross et al., 2016). GET-RGE relies on measuring minute ventilation, V_{O2}, and V_{CO2} productions, during a traditional exercise test, such as treadmilling, cycle ergometer, arm crank, etc. (Albouaini et al., 2007; Orr et al., 2013; Ross et al., 2016). However, methods using GET-RGE are typically expensive and require training to use, are time-consuming, can be unpleasant, and are thus not feasible to assess CRF on larger scales (Ross et al., 2016). CRF can be estimated without measuring gas exchange, from an incremental test to exhaustion which utilizes the maximum work rate (ITE-MWR), to estimate VO_{2max} (Andersen, 1995; Beltz et al., 2016). Although ITE-MWR is also very unpleasant, time-consuming, and requires the

participant to be able to exert maximum effort when performing the test (Malek et al., 2004b; Noonan and Dean, 2000; Ross et al., 2016). In contrast, submaximal exercise testing is a less unpleasant procedure for estimating VO_{2max}, which does not require the participants to exert maximal effort (Noonan and Dean, 2000; Zepetnek et al., 2015). Submaximal testing can estimate CRF, from the relationship between heart rate (HR) and work rate, although this is not as precise at estimating CRF, as ITE-MWR- or GET-RGE tests, and is still time-consuming (Ross et al., 2016).

A non-exercise prediction equation (NEPE), is a cheap, fast, and easy method that often does not require much equipment, physical activity (PA), and trained personnel (Malek et al., 2004a; Peterman et al., 2019). However, present NEPEs have low accuracy (R^2 = 0.50 - 0.86, SEE = 2.98 - 6.90 $mL \cdot kg^{-1} \cdot min^{-1}$) and are thus not recommended as an alternative for the assessment of CRF (Ross et al., 2016). A possible explanation for the low accuracy of NEPEs could be due to the parameters used when developing the equations. Most NEPEs typically estimates CRF from demographic data, such as BMI, age, and sex (Peterman et al., 2020, 2019). A review by Peterman et al. (2020) found that physical activity (PA) is an important parameter in predicting VO_{2max} in AB, but a source of error in the present models is that they predominantly use self-reported PA as opposed to objective measures of PA (Peterman et al., 2020). Thus, adding objective physiological measures relating to PA and training level might improve the accuracy of NEPEs. Cardiac output is a large contributor to VO_{2max}, following PA (Murias et al., 2010). Consequently adding intrinsic cardiac measurements to NEPE might improve the accuracy.

Much of the variance in VO_{2max} relates to cardiac structures that can be measured at rest, eg. left ventricular (LV) mass and end-diastolic volume (EDV) (La Gerche et al., 2012). A new study investigated the use of intrinsic cardiac measurements at rest, obtained using seismocardiography (SCG) for estimating VO_{2max} (Sørensen et al., 2020). SCG was first developed by Mounsey (1957) and is a method of measuring cardiac vibrations, by placing an accelerometer on the sternum. Electrocardiogram, echocardiogram, and phonocardiogram have been used to correlate fiducial points in these vibrations to certain cardiac events eg. mitral- and aortic valve opening and closing (Mounsey, 1957; Sørensen et al., 2020). Adding measurements from SCG to a NEPE, Sørensen et al. (2020) found an improvement in accuracy of the developed NEPE, from R = .80 (95%-CI: .67 - .88) including only demographic measurements to R = .90 (95%-CI: .83 - .94) with the addition of SCG measurements.

Sørensen et al. (2020) also investigated if their NEPE could monitor training-induced changes in VO_{2peak}, from eight weeks of combined cardio-respiratory- and weight-lifting training, in healthy women. Assessing CRF regularly during eg. physical interventions can help clinicians assess changes in risk of CVD, and monitor the effects of rehabilitation programs (Lang et al., 2018; Ross et al., 2016).
Sørensen et al. (2020) found their model to accurately classify the direction of change in VO_{2peak} in just 58.8% of participants. The authors suggested that a possible explanation for these results could be due to the training intervention not being adequate to elicit myocardial adaptations, which would possibly change SCG measurements (Convertino et al., 1980; Sørensen et al., 2020). A recent study investigated 27 different NEPE's ability to predict longitudinal changes to CRF, in AB (Peterman et al., 2020). The study found that NEPEs could correctly classify a positive-, negative- or no change in CRF 56% of the time, with a range of 31 - 61% (Peterman et al., 2020). Thus the detection of longitudinal changes obtained by Sørensen et al. (2020) is relatively average, compared to other NEPEs.

To our knowledge, no NEPE for individuals with SCI has been developed. Consequently, the first aim of this study is to investigate if a NEPE specific for individuals with SCI can be developed. Secondly, this study aims to compare a developed NEPE for individuals with SCI (SCI-NEPE), to present NEPEs for AB (AB-NEPE) (Baynard et al., 2016; Myers et al., 2017; Sørensen et al., 2020). Relevant parameters typically available for routine clinical visits, as well as SCG measurements, will be investigated as SCI-NEPE predictors, so CRF can be easily assessed, and used as a clinical vital sign, as suggested by Ross et al. (2016). Thirdly, this study seeks to examine if a SCI-NEPE can predict exercise-induced changes in VO_{2peak}, after a six week training period. Finally, to our knowledge, there are no studies that have directly investigated the relationship between training-induced changes in VO_{2peak} and changes in SCG, thus the present study examines this correlation.
We hypothesize that a population-specific NEPE, developed on a sample of individuals with SCI, with age between 18 and 70 years, will outperform other AB-NEPEs developed for AB, applied on the investigated SCI sample.

Method

Due to the ongoing pandemic of COVID-19, the authors of the present study were prevented from performing experimental work at the University of Aalborg. Instead, the data has been provided and collected by Ph.D. student Rasmus Kopp Hansen, as part of his Ph.D. study, regarding the effects of a training intervention on individuals with SCI (Hansen et al., 2020).

Participants

18 participants (males = 11) were recruited through; notices at Aalborg University, via websites for recruiting volunteers (eg, www.forsog.dk), organizations for individuals with SCI and other disabilities (eg, Spinal Cord Injured in Denmark organization), and active recruiting at local physician clinics.
Inclusion criteria for participants were: Males and females with age between 18 - 70 years, have had a chronic SCI for >1 year, physically able to perform upper body rowing, and use a manual wheelchair as a primary mobility tool.
Exclusion criteria for participants were: No shoulder operation within the last year, no cortisone injection within the last four months, no known history of diabetes or known diseases that could impair the ability to perform physical activity, or any known medical issues.
Additionally, the participants' SCI lesion-level were classified according to international standards for neurological classification of spinal cord injury (ISNCSCI) (Kirshblum et al., 2011), by a medical doctor with a specialization in SCI. Furthermore, the participants gave information about: Smoking habits, medical issues, diseases, or medication that could affect metabolism or the cardiovascular system.

Study design

The study design consisted of two parts. Part one's main focus was to develop a SCI-NEPE and test the present AB-NEPEs (Baynard et al., 2016; Myers et al., 2017; Sørensen et al., 2020), on individuals with SCI. The SCI-NEPE and AB-NEPE were then compared. In part two, the main focus was to determine if the developed SCI-NEPE from part one could be used to detect a change in VO_{2peak} after a six-week training period. Additionally, it was investigated if there was a correlation between training-induced changes in VO_{2peak} and changes in measured variables.

Part one

The first part of the study consisted of a baseline (BL) laboratory trial day. The experimental protocol at BL and at six-week follow-up test (6W) were similar and were performed at the same time of day (±1,98 hours) for each participant, to avoid time of day variability. Beforehand participants were asked to avoid; strenuous exercise >24 hours before the trial; caffeine, alcohol, vitamin C, polyphenols, and any other substance known to affect the cardiovascular system >12 before the trial; any smoking >6 hours before the trial and any

food intake (fasting) >3 hours before the trial. Furthermore, if participants were taking any medication, participants were asked to discontinue use of the drug at least 4 - 5 times the half-life time of the drug, although if the medication, due to health issues, could not be safely withdrawn, the trial testing was performed within a consistent time-period after the medication intake. Before any test was performed, participants were asked to empty their bladder. During the test day, the participants were free to drink water as needed.

Laboratory measurements

Blood pressure and resting heart rate

Following an initial rest of 10 minutes after arrival, the participant's blood pressure (BP) and resting heart rate (RHR) were measured, with a sphygmomanometer (OMRON M3, OMRON Healthcare, Hoofddorp, Netherlands). Measurements were taken twice, consistently on the same arm, with the participants in a sitting position. If measurements deviated > 5% a third measurement was conducted. Mean arterial pressure (MAP) was calculated from BP values (⅔ diastolic + ⅓ systolic). The lowest systolic, diastolic, MAP, and RHR values were used as model parameters.
There was a problem measuring RHR from one participant with the sphygmomanometer as the participant was found to have extremely high BP due to kidney problems, and the apparatus couldn't provide an output. Instead, the minimum average RHR, and BP over an interval of 10 seconds measured by a finger plethysmograph (Finometer, Finapres Medical Systems BV, Enschede, the Netherlands) with the participants in a supine position were used as the reported values.

Anthropometric measurements

The participants' body mass was measured while sitting in their wheelchair in light exercise clothing using a wheelchair scale (Detecto 6550 wheelchair scale, Webb City, Missouri, USA). Participants' body mass was then calculated by subtracting the weight of the wheelchair, from the prior measurement, rounded to the nearest 0.1 kg.
Participants' height was measured from the heel to the top of the skull, with the participants in supine position. For participants with contractures, segmented measurements were taken and summed.
Waist circumference (WC) and hip circumference (HC) were measured with non-elastic tape in a supine position, below the lowest rib (waist) and widest part of the trochanters (hip), following a deep exhalation, with participants' arms placed by the side.
Height, WC, and HC were all rounded to the nearest 0.1 cm and measured twice, with a third

measurement performed if there was a >0.1 cm difference. The mean of the two or three measurements was used as the reported value.
Weight [kg], height [m], BMI (weight [kg] / height^2 [m]), WC [cm], HC [cm] and waist-hip ratio were used as possible NEPE variables.

Leisure-time physical activity

Leisure-time activity was examined with the leisure-time physical activity questionnaire for people with spinal cord injury (LTPA) (Martin Ginis et al., 2012). LTPA is a method to investigate self-determined PA-level for an individual with SCI. The LTPA examines the last seven days, divided into mild, moderate, and heavy activity. Mild, moderate, heavy, and total LTPA, measured in min/week, were used as possible NEPE variables.

Spinal cord injury lesion-level

Participants provided a copy of their medical record, which included their SCI lesion-level, as well as the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Kirshblum et al., 2011). The injury-level was used as a parameter to develop SCI-NEPE, and AIS for a Table [lesion-level ≥ T6-level = 0; lesion-level < T6-level = 1].

Seismocardiography

SCG measurements were obtained according to guidelines from Sørensen et al. (2018/2020). An accelerometer (Model 1521-002, Silicon Design, Seattle Washington, USA), placed inside a plastic casing (19 x 21 x 11 mm), with a resolution of ±2 g, low noise at 7 μ / √Hz and frequency response 0 - 300 Hz, was placed on the xiphoid process with double adhesive tape. SCG was recorded over 5 minutes with participants resting in the supine position, using IWorx IX-228/s (iWorx, Dover, New Hampshire, USA) data acquisition unit, with a 5000 Hz acquisition unit sampling, connected to a Laptop with LabScribe recording software (version 3., iWorx, Dover, New Hampshire, USA).

Seismocardiography signal processing

SCG-signal processing was performed by VentriJect (VentriJect, Hellerup, Denmark), using an automatic algorithm for finding the fiducial points, and peak-to-peak values described in Sørensen et al. (2018). Afterward, the marked fiducial points were manually and visually inspected, to confirm if they were marked correctly. Figure 1 illustrates points marked by the algorithm.

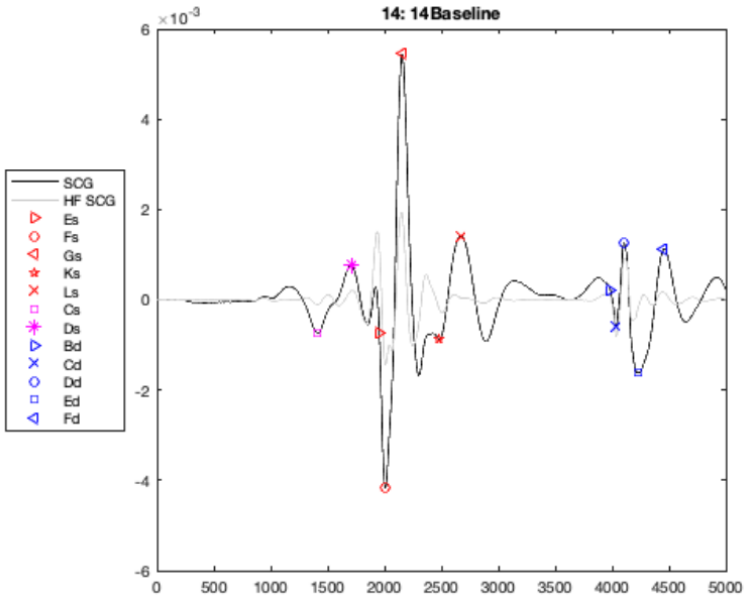


Figure 1: Example of a SCG signal after processing and marked fiducial points, by an automated algorithm developed by Sørensen et al. (2020). The x-axis shows time [µs] and Y-axis shows SCG [mg].

SCG measurements were given as amplitudes for each fiducial point in micro acceleration [mg], as well as differences between selected amplitudes, as described by Sørensen et al. (2018). amp_Cd_to_Dd is eg. calculated as follows: amp_Cd_to_Dd = (amp_Dd) ÷ (amp_Cd).

Peak oxygen uptake

Peak oxygen uptake (VO_{2peak}) was measured during an incremental arm-crank test to exhaustion. Before the test, the participants shoulder joint was aligned with the crank axis on the ergometer (Monark 881E, Monark Exercise, Vansbro, Sweden) with their elbow slightly bent. Participants were then equipped with a facemask, connected to an online open-circuit metabolic cart (JAEGER, Vyntus CPX, Carefusion, Chicago, USA) which was calibrated according to manufactural guidelines in terms of known volumes and gas concentrations. The incremental test was initiated, after a one-minute zero-resistance warm-up, with an individualized starting load between 0 - 50 W, with an increasing workload of 3.5 or 7 W (depending on lesion-level) per minute until exhaustion; i.e. unable to maintain a cadence of >60 RPM. The individualized resistance was based on the questioning of training history, lesion-level, and dialogue during warmup, with an aim of reaching exhaustion between 8 - 12 min, at a 70 RPM cadence throughout the trial (Eerden et al. 2018). Breath-by-breath VO_2 and VCO_2 were measured throughout the test, and VO_{2peak} was reported as the highest

average 15 s interval during the test (mL O_2/kg/min). This value was then used as the dependent variable in the model.

Blood sample

A ~50 mL blood sample from the median cubital vein was taken from the participants, on a separate day, (± 7 days of BL and 36 - 60 hours after the last exercise intervention session) from the laboratory test day, after >10 hours of fasting. The blood samples were stored at -80°C, at Aalborg University Hospitals Department of Biochemistry, pending analysis. Hemoglobin A_{1c} (HbA_{1c}), and ß-hemoglobin from the analysis were used as possible NEPE variables.

Non-exercise prediction equation development

BL-data, illustrated in Figure 2, was used as input in a multiple linear forward and backward stepwise regression (SWR), to develop the SCI-NEPEI. The SWR was performed using the built-in function in SPSS (IBM SPSS Statistic version 27, New York, USA). The SWR was set to include (step-up) or remove (step-down) the independent variables from the model, based on the statistical significance of the change in the sum of squared errors. The criteria for each variable to be added was $p < .05$ and removal was $p > .10$ (Sørensen et al., 2020). The process was repeated until no more parameters could be added or removed from the model.

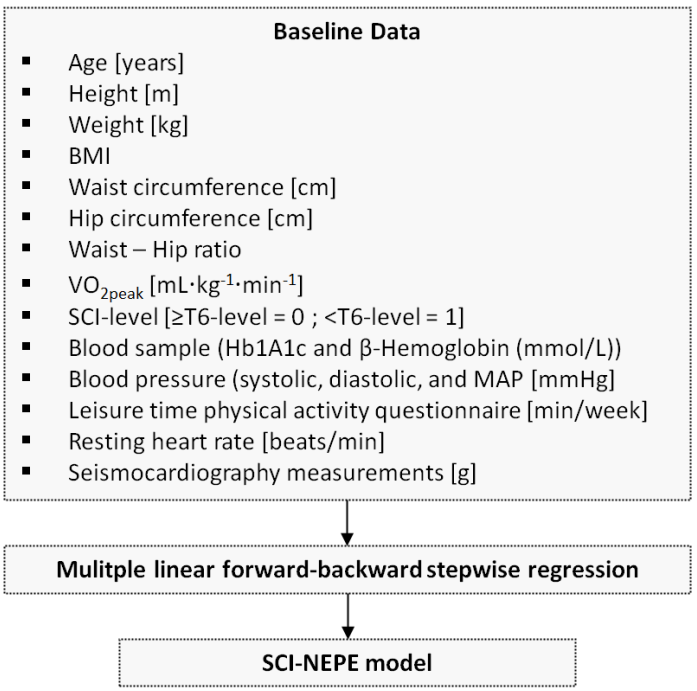


Figure 2: Development of SCI-NEPE from collected BL-data by multiple linear forward-backward stepwise regression.

Comparison between non-exercise prediction equations

For comparison of SCI-NEPE, three AB-NEPEs were chosen: Baynard et al. (2016), Myers et al. (2017), and Sørensen et al. (2020). The three AB-NEPEs are represented in Table 1.

Table 1: AB-NEPEs used for comparison to SCI-NEPEs. BMI = body mass index. Pearson's correlation (R) and standard error of estimate (SEE) [mL·kg^{-1}·min^{-1}] are presented for all AB-NEPE.

Authors	Equation	R	SEE
Sørensen et al. 2020	44.1 – 0.465·BMI + 6.79·sex (m=1; w=0) – 0.187·age [years] + 0.292·Acpp [mg]	.90	3.18
Baynard et al. 2016	88.35 − 14.79·sex (m=0; w=1) − 0.40·WC [cm] − 0.27·age [years]	.77	6.70
Myers et al. 2017	79.9 - 0.39·age [years] - 13.7·sex (m=0; w=1) - 0.127·weight [lbs]	.79	7.20

Part two

Half of the participants were randomly assigned to a six week training intervention, and the other half of the participants acted as a control group, seen in Figure 3. After the six week training intervention, laboratory measurements were repeated at 6W. The AB-NEPEs from the literature, and the SCI-NEPE developed from BL-data, were then used to examine if they could predict, and if so, how well they could predict a change in VO_{2peak}, after a six week training intervention. Changes in all variables were then investigated for correlation to changes in VO_{2peak}.

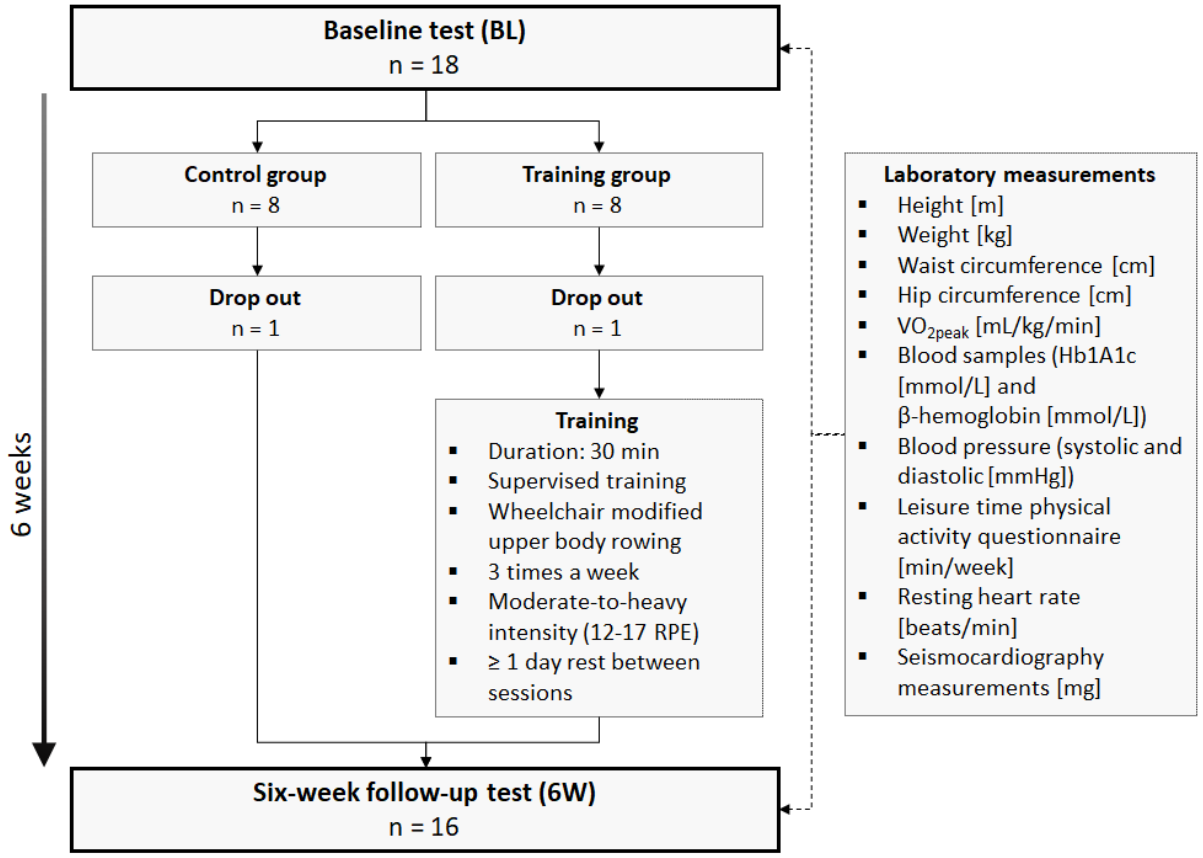


Figure 3: After the BL, the participants were randomly grouped into control or training. There was one drop out from each group. The training group underwent 3 training sessions per week with ≥ 1 day rest between sessions. Six weeks after BL a 6W, identical to the BL, was performed.

Exercise intervention

The exercise intervention, depicted on Figure 3, consisted of 30 minutes moderate-to-heavy intensity (rating of perceived exertion 12 - 17 on the BORG scale (Borg, 1998)) wheelchair modified upper-body rowing, three times per week, with ≥ 1 day rest between sessions. The participants were intended to perform 6 x 5 bouts of exercise with a 1 - 2 minutes rest between bouts, although the exercise duration was individually tailored to accommodate large differences in functional levels and physical capacity of the participants. The exercise had a gradual increase in intensity over time, to facilitate a continuous increase in fitness level. The exercise protocol was in line with current exercise recommendations for SCI individuals (Hansen et al., 2020).

Statistics

The statistics in the present study were calculated using SPSS (IBM SPSS Statistic version 27, New York, USA), with an alpha level of $p < .05$.

Part one

To evaluate the developed SCI-NEPE in the present study and compare them to the three AB-NEPE from the literature, Pearson's Correlation (R) and coefficient of determination (R^2), standard error of estimate (SEE), and percentage SEE (%SEE), was calculated for each SCI-NEPE and AB-NEPE:

$$SEE = \sqrt{\Sigma(Y - \widehat{Y})^2/n - 2}$$

$$\%SEE = SEE/(\Sigma\widehat{Y}/n) * 100$$

Y is the measured VO_{2peak}, and $\hat{Y}$ is the estimated VO_{2peak}

Part two

A mixed model analysis of variance was used to test if there were interaction between groups (control and training) and time (BL and 6W), and differences between BL and 6W in each group, for all continuous variables. Independent t-tests were performed between groups, for BL variables (for all continuous variables), to test for differences.

The developed SCI-NEPEs and AB-NEPEs, were tested for if they could predict whether the VO_{2peak} changed positively or negatively, in the training group. Predicted direction of change (PDOC), was calculated by dividing the number of correctly classified individuals , by the total number of individuals in the training group, and is given in %. An individual was classified correctly, if they eg. had a positive change in VO_{2peak}, and the NEPE predicted a positive change as well, regardless of magnitude of change.

Pearson's Correlation coefficient (R) and coefficient of determination (R^2) were performed on the differences (Δ) between all measured continuous variables and the differences between measured VO_{2peak} (ΔVO_{2peak}), between BL and 6W.

Results

Part one

Table 2: All measured variables used for development of SCI-NEPE from BL-data. Sex and American Spinal Injury Assosiation Imparirment Scale (AIS) are presented as the number of cases in each group. SCI lesion-level is presented with range and the rest of the variables with mean ± standard deviation (SD). One participant, who dropped out after BL was not classified with AIS and SCI lesion level (Δ).

Baseline test (BL) (total n = 18)

Clinical measurements		Seismocardiography (SCG)	
Sex	Male = 11		
SCI lesion level [range]	C4 - L3		
ASIA [A-D] Δ	A = 7 B = 1 C = 8		
	Mean ± SD		Mean ± SD
Age [years]	49.6 ± 8.7	amp_Dd [mg]	2.5 ± 1.3
Height [m]	1.76 ± 0.12	amp_Cd [mg]	-0.9 ± 0.8
Weight [kg]	83.1 ± 15.2	amp_Ed [mg]	-2.6 ± 1.2
BMI [kg/m^2]	27.0 ± 5.9	amp_Fd [mg]	0.9 ± 0.8
Low LTPA [min/week]	430.7 ± 847.3	amp_Gs [mg]	3.0 ± 2.0
Moderate LTPA [min/week]	94.1 ± 151.5	amp_Fs [mg]	-3.1 ± 1.8
High LTPA [min/week]	42.0 ± 78.8	amp_KS [mg]	-2.4 ± 1.1
Moderate + high LTPA [min/week]	136.1 ± 209.8	amp_Ls [mg]	2.1 ± 1.1
Total LTPA [min/week]	566.8 ± 881.5	amp_Bd [mg]	0.1 ± 0.4
Systolic [mmHg]	130.1 ± 29.3	amp_Ds [mg]	1.0 ±0.6
Diastolic [mmHg]	80.3 ± 16.1	amp_Cs [mg]	-0.7 ± 0.3
MAP [mmHg]	96.9 ± 19.9	amp_Cd_to_Dd [mg]	3.4 ± 1.7
Resting heart rate [beats/min]	65.6 ± 10.7	amp_Fs_to_Gs [mg]	6.1 ± 3.6
Waist [cm]	99.2 ± 16.2	amp_Gs_to_KS [mg]	5.3 ± 2.5
Hip [cm]	104.9 ± 8.6	amp_Ls_to_KS [mg]	4.4 ± 2.1
Waist - hip ratio	0.9 ± 0.1	amp_Dd_to_Ed [mg]	5.1 ± 2.2
Hb1A1c [mmol/L]	32.8 ± 3.6	amp_Fd_to_Ed [mg]	3.4 ± 1.7
β-Hemoglobin [mmol/L]	8.51 ± 0.82	amp_Cd_to_Ed [mg]	1.6 ± 1.5
VO_{2peak} [mL·kg^{-1}·min^{-1}]	17.7 ± 7.4	Δ 1 person not classified	

18 participants were recruited for the study. In Table 2, the collected variables from BL are depicted with mean and standard deviation, number of cases or range.

Based on the data collected at BL (Table 2), seven SCI-NEPEs were developed, with SWR, and presented with β-coefficients, as seen in Figure 4.

$$SCI\text{-}NEPE\text{-}M1: VO_{2peak} = 8.351 + (2858.192 \cdot amp\_Fd\_to\_Ed)$$

$$SCI\text{-}NEPE\text{-}M2: VO_{2peak} = 49.083 + (2467.508 \cdot amp\_Fd\_to\_Ed) + (-0.376 \cdot hip)$$

$$SCI\text{-}NEPE\text{-}M3: VO_{2peak} = 46.6 + (2202.814 \cdot amp\_Fd\_to\_Ed) + (-0.378 \cdot hip) + (5.182 \cdot lesion\text{-}level)$$

$$SCI\text{-}NEPE\text{-}M4: VO_{2peak} = 55.440 + (2354.191 \cdot amp\_Fd\_to\_Ed) + (-0.321 \cdot hip) + (5.836 \cdot lesion\text{-}level) + (-0.237 \cdot RHR)$$

$$SCI\text{-}NEPE\text{-}M5: VO_{2peak} = 56.149 + (3334.051 \cdot amp\_Fd\_to\_Ed) + (-0.342 \cdot hip) + (6.237 \cdot lesion\text{-}level) + (-0.2 \cdot RHR) + (-2230.822 \cdot amp\_Ls)$$

$$SCI\text{-}NEPE\text{-}M6: VO_{2peak} = 59.894 + (3743.074 \cdot amp\_Fd\_to\_Ed) + (-0.411 \cdot hip) + (5.773 \cdot lesion\text{-}level) + (-0.144 \cdot RHR) + (-2658.839 \cdot amp\_Ls) + (-4139.568 \cdot amp\_Bd)$$

$$SCI\text{-}NEPE\text{-}M7: VO_{2peak} = 33.06 + (3535.801 \cdot amp\_Fd\_to\_Ed) + (-0.446 \cdot hip) + (8.438 \cdot lesion\text{-}level) + (-0.082 \cdot RHR) + (-2844.768 \cdot amp\_Ls) + (-4621.396 \cdot amp\_Bd) + (14.632 \cdot height)$$

Figure 4: Shows all seven developed SCI-NEPE with β-coefficients. RHR = Resting heart rate [beats/min], hip = hip circumference [cm], all SCG measurements (amp_) are presented as [mg], and lesion-level is presented as [lesion-level ≥ T6-level = 0; lesion-level < T6-level = 1].

R and R^2, SEE, and %SEE were calculated for each model, and are presented in Table 3. The AB-NEPEs are likewise presented with R, R^2, SEE and %SEE in Table 3. All of the SCI-NEPEs have a significant R ($p < .01$) and lower SEE, compared to the AB-NEPEs. The best SCI-NEPE is SCI-NEPE-M7 with a R = .992 ($p < .01$, SEE 0.968 [$mL \cdot kg^{-1} \cdot min^{-1}$]). None of the AB-NEPEs correlates ($p > .05$) significantly with measured VO_{2peak}.

Table 3:SCI-NEPEs developed on BL-data, as well as the AB-NEPEs, are presented with Pearson's correlation (R), coefficient of determination (R^2), standard error of estimates (SEE), and percentage SEE (%SEE).

	Baseline			
	R	R^2	SEE [mL·kg^{-1}·min^{-1}]	%SEE [%]
SCI-NEPE-M1	.685**	0.47	5.456	29.880
SCI-NEPE-M2	.813**	0.66	4.366	23.980
SCI-NEPE-M3	.877**	0.769	3.601	19.724
SCI-NEPE-M4	.930**	0.865	2.758	15.123
SCI-NEPE-M5	.961**	0.923	2.083	11.432
SCI-NEPE-M6	.983**	0.967	2.597	12.784
SCI-NEPE-M7	.992**	0.983	0.968	5.281
Sørensen et al., 2020	.242	0.059	11.474	44.032
Baynard et al., 2016	.351	0.123	13.830	50.864
Meyers et al., 2017	.295	0.087	16.644	52.921

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.01 level.

Part two

16 participants were measured at 6W, where half of the participants had undergone a six week training intervention (n = 8), and half of the participants acted as controls (n = 8). Table 4A, depicts clinical measurements for control and training group respectively, at BL and 6W. Table 4B predicts SCG measurements at BL and 6W, for control and training group, respectively. VO_{2peak} for the training group was the only variable that significantly changed from BL to 6W ($p < .05$).

*Table 4:). All measurements from BL and 6W are depicted in respects to the control- and training group. Significant differences ($p < .05$) are highlighted with bold text and a " ***** ".*
***A**: Depicts all clinical measurements. Sex and American Spinal Injury Assosiation Imparirment Scale (AIS) are shown presented as the number of cases in each group, SCI lesion level with range and the rest of the variables with mean ± standard deviation (SD)*
***B**: Depicts all SCG measurements.with mean ± standard deviation (SD)*

Baseline test (BL) - six-week follow-up test (6W)

A — **Clinical measurements**

	Control (n = 8)		Training (n = 8)	
Sex	Male = 4		Male = 5	
SCI lesion level [range]	C4 - L3		C6 - L2	
ASIA [A-D]	A = 5 B = 0 C = 3		A = 3 B = 1 C = 4	
	Baseline	6W follow-up	Baseline	6W follow-up
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age [years]	50.0 ± 12.3	50.0 ± 12.3	49.6 ± 4.3	49.6 ± 4.3
Height [m]	1.77 ± 0.11	1.77 ± 0.11	1.75 ± 0.14	1.75 ± 0.1
Weight [kg]	78.9 ± 18.2	79.2 ± 17.8	86.7 ± 12.5	86.0 ± 12.7
BMI [kg/m^2]	25.4 ± 6.2	25.5 ± 6.1	28.6 ± 5.7	28.4 ± 5.8
Low LTPA [min/week]	759.1 ± 1208.2	105.9 ± 101.1	161.3 ± 242.1	233.1 ± 322.7
Moderate LTPA [min/week]	100.5 ± 215.5	173.8 ± 356.0	70.0 ± 84.1	100.0 ± 96.4
High LTPA [min/week]	44.5 ± 78.5	45.0 ± 75.2	46.3 ± 92.9	53.8 ± 91.5
Moderate + high LTPA [min/week]	145.0 ± 283.7	218.8 ± 423.5	116.3 ± 159.0	153.8 ± 155.8
Total LTPA [min/week]	904.1 ± 1234.1	324.7 ± 514.5	277.5 ± 352.9	386.9 ± 384.5
Systolic [mmHg]	126.6 ± 20.5	127.9 ± 25.1	130.4 ± 40.1	125.9 ± 25.8
Diastolic [mmHg]	80.6 ± 11.9	80.3 ± 14.5	81.1 ± 22.0	76.6 ± 16.3
MAP [mmHg]	96.0 ± 14.5	96.1 ± 17.8	97.5 ± 27.3	93.0 ± 19.3
Resting heart rate [beats/min]	68.1 ± 7.8	66.0 ± 11.8	65.6 ± 13.4	65.1 ± 11.7
Waist [cm]	92.7 ± 12.4	92.4 ± 11.9	106.7 ± 17.5	101.5 ± 14.5
Hip [cm]	105.3 ± 10.3	103.8 ± 9.8	105.6 ± 7.4	105.1 ± 6.6
Waist - hip ratio	0.9 ± 0.1	0.9 ± 0.0	1.0 ± 0.2	1.0 ± 0.1
Hb1A1c [mmol/L]	31.9 ± 2.1	32.0 ± 1.2	33.9 ± 4.8	33.5 ± 4.3
β-Hemoglobin [mmol/L]	8.65 ± 0.35	8.65 ± 0.38	8.25 ± 1.1	8.36 ± 1.2
VO_{2peak} [mL·kg^{-1}·min^{-1}]	16.9 ± 5.7	16.6 ± 6.2	15.4 ± 5.1	**16.8*** ± 5.2

B	Seismocardiography (SCG)			
	Control (n = 8)		Training (n = 8)	
	Baseline	6W follow-up	Baseline	6W follow-up
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
amp_Dd [mg]	2.5 ± 0.7	2.4 ± 0.7	2.3 ± 1.6	2.5 ± 1.6
amp_Cd [mg]	-1.0 ± 0.7	-1.5 ± 0.7	-1.0 ± 1.0	-1.9 ± 2.1
amp_Ed [mg]	-2.4 ± 1.2	-2.7 ± 1.1	-2.6 ± 1.2	-1.8 ± 1.3
amp_Fd [mg]	0.7 ± 0.7	0.5 ± 0.3	0.9 ± 0.5	0.7 ± 0.6
amp_Gs [mg]	3.3 ± 1.9	4.3 ± 1.0	2.8 ± 2.3	2.6 ± 1.8
amp_Fs [mg]	-3.5 ± 1.2	-4.2 ± 1.8	-2.8 ± 2.3	-3.2 ± 2.0
amp_KS [mg]	-1.9 ± 1.3	-2.2 ± 0.8	-2.6 ± 0.5	-2.4 ± 0.9
amp_Ls [mg]	1.8 ± 0.8	2.1 ± 0.7	2.5 ± 1.2	2.4 ± 1.6
amp_Bd [mg]	0.1 ± 0.5	0.0 ± 0.4	0.1 ± 0.4	0.3 ± 0.6
amp_Ds [mg]	0.7 ± 0.2	0.6 ± 0.2	1.3 ± 0.8	1.2 ± 0.5
amp_Cs [mg]	-0.7 ± 0.4	-0.9 ± 0.4	-0.7 ± 0.3	-1.3 ± 1.0
amp_Cd_to_Dd [mg]	3.5 ± 0.8	3.9 ± 1.1	3.3 ± 2.4	4.4 ± 3.4
amp_Fs_to_Gs [mg]	6.8 ± 2.9	8.5 ± 3.7	5.6 ± 4.5	5.8 ± 3.5
amp_Gs_to_KS [mg]	5.2 ± 2.9	6.5 ± 2.6	5.4 ± 2.3	5.1 ± 2.0
amp_Ls_to_KS [mg]	3.7 ± 1.9	4.3 ± 1.1	5.1 ± 1.7	4.8 ± 2.3
amp_Dd_to_Ed [mg]	4.9 ± 1.7	5.1 ± 1.6	4.9 ± 2.4	4.2 ± 2.6
amp_Fd_to_Ed [mg]	3.1 ± 1.6	3.2 ± 1.3	3.5 ± 1.4	2.5 ± 1.6
amp_Cd_to_Ed [mg]	1.4 ± 1.7	1.2 ± 1.0	1.6 ± 1.3	-0.1 ± 2.7

The SCI-NEPEs and AB-NEPEs were used on the data from 6W. R and R^2, SEE, and %SEE were calculated for each model are presented in Table 5. PDOC [%] for the training group was calculated, and is presented in Table 5.

The SCI-NEPEs show significant correlations, when predicting VO_{2peak} at 6W ($p < .05$). The best SCI-NEPE for predicting VO_{2peak} at 6W is SCI-NEPE-M3 ($R = .787$, $p < .01$, SEE = 4.0 [$mL \cdot kg^{-1} \cdot min^{-1}$]), and the worst SCI-NEPE is SCI-NEPE-M7 ($R = .606$, $p < .05$, SEE = 6.5 [$mL \cdot kg^{-1} \cdot min^{-1}$]). The AB-NEPEs were not significantly correlated with measured VO_{2peak} ($p > .05$).

The best SCI-NEPE at PDOC is SCI-NEPE-M5 (PDOC = 57%) and the worst is SCI-NEPE-M7 (PDOC = 0%). The AB-NEPE with the best PDOC is Sørensen et al. (2020) (PDOC = 100%).

Table 5: The seven SCI-NEPEs and three AB-NEPEs from the literature, were tested for predicting VO_{2peak} after six weeks. Pearson's correlation (R), coefficient of determination (R^2), standard error of estimates (SEE), and percentage SEE (%SEE), and the predicted direction of change (PDOC) are presented.

	6W follow-up				
	R	R^2	SEE [mL·kg^{-1}·min^{-1}]	%SEE [%]	PDOC [%]
SCI-NEPE-M1	.618*	.382	17.9	108.0	25
SCI-NEPE-M2	.634**	.634	5.0	29.5	29
SCI-NEPE-M3	.787**	.619	4.0	23.7	29
SCI-NEPE-M4	.762**	.581	4.0	24.0	43
SCI-NEPE-M5	.711**	.506	5.2	27.6	57
SCI-NEPE-M6	.608*	.370	6.4	41.7	14
SCI-NEPE-M7	.606*	.367	6.5	42.2	0
Sørensen et al., 2020	-.166	.028	13.1	50.1	100
Baynard et al., 2016	-.06	.004	18.2	61.2	75
Meyers et al., 2017	-.124	.015	18.8	59.8	0

* Correlation is significant at the 0.05 level.

** Correlation is significant at the 0.01 level.

The correlation between changes in VO_{2peak} and changes in clinical- and SCG measurements, from BL to 6W, was investigated for both total, control, and the training group. △Moderate LPTA and △Moderate + heavy LTPA, show significant correlations with the changes in VO_{2peak} ($p < .05$), in the control group. Seven measures from the SCG signal (△amp_Dd, △amp_Cd, △amp_Gs, △amp_Cs, △amp_Cd_to_Dd, △amp_Gs_to_Ks, and △amp_Cd_to_Ed), correlates significantly ($p < .05$) with changes in VO_{2peak} in the training group. No correlation was found when investigating the group of total participants.

*Table 6: Pearson's correlation (R) between the change (△) in VO_{2peak} and the change (△) in clinical measurements, from BL to 6W. Significant changes is indicated with bold and " * ".*

	Total		Control		Træning	
	$\triangle VO_{2peak}$ (n = 16)		$\triangle VO_{2peak}$ (n = 8)		$\triangle VO_{2peak}$ (n = 8)	
	Pearson Correlation	p-value	Pearson Correlation	p-value	Pearson Correlation	p-value
$\triangle VO_{2peak}$	1.000		1.000		1.000	
△Weight (kg)	-.056	.837	.207	.624	.042	.922
△BMI	-.087	.749	.182	.666	-.090	.832
△Low LTPA (min/week)	.142	.600	-.091	.830	-.246	.556
△Moderate LTPA (min/week)	.421	.105	**.767***	.026	.070	.869
△Heavy LTPA (min/week)	.216	.422	.213	.613	.242	.564
△Moderate + heavy LTPA (min/week)	.441	.087	**.791***	.019	.136	.749
△Total LTPA	.198	.462	.000	1.000	-.184	.662
△Systolic	-.197	.465	-.144	.735	-.209	.619
△Diastolic	-.189	.482	-.041	.923	-.073	.864
△MAP	-.220	.412	-.088	.836	-.175	.679
△Resting heart rate	-.006	.983	-.061	.886	-.114	.788
△Waist circumference	-.182	.501	.128	.763	.058	.892
△Hip circumference	.096	.725	.404	.321	-.279	.503
△Waist - hip ratio	-.031	.910	-.118	.780	-.296	.476
$\triangle HB1A_{1c}$	-.069	.801	.300	.471	-.548	.159
△B-hemoglobin	.107	.694	.046	.913	-.065	.878

*** Correlation is significant at the .05 level**

△ change from baseline to 6 week follow-up

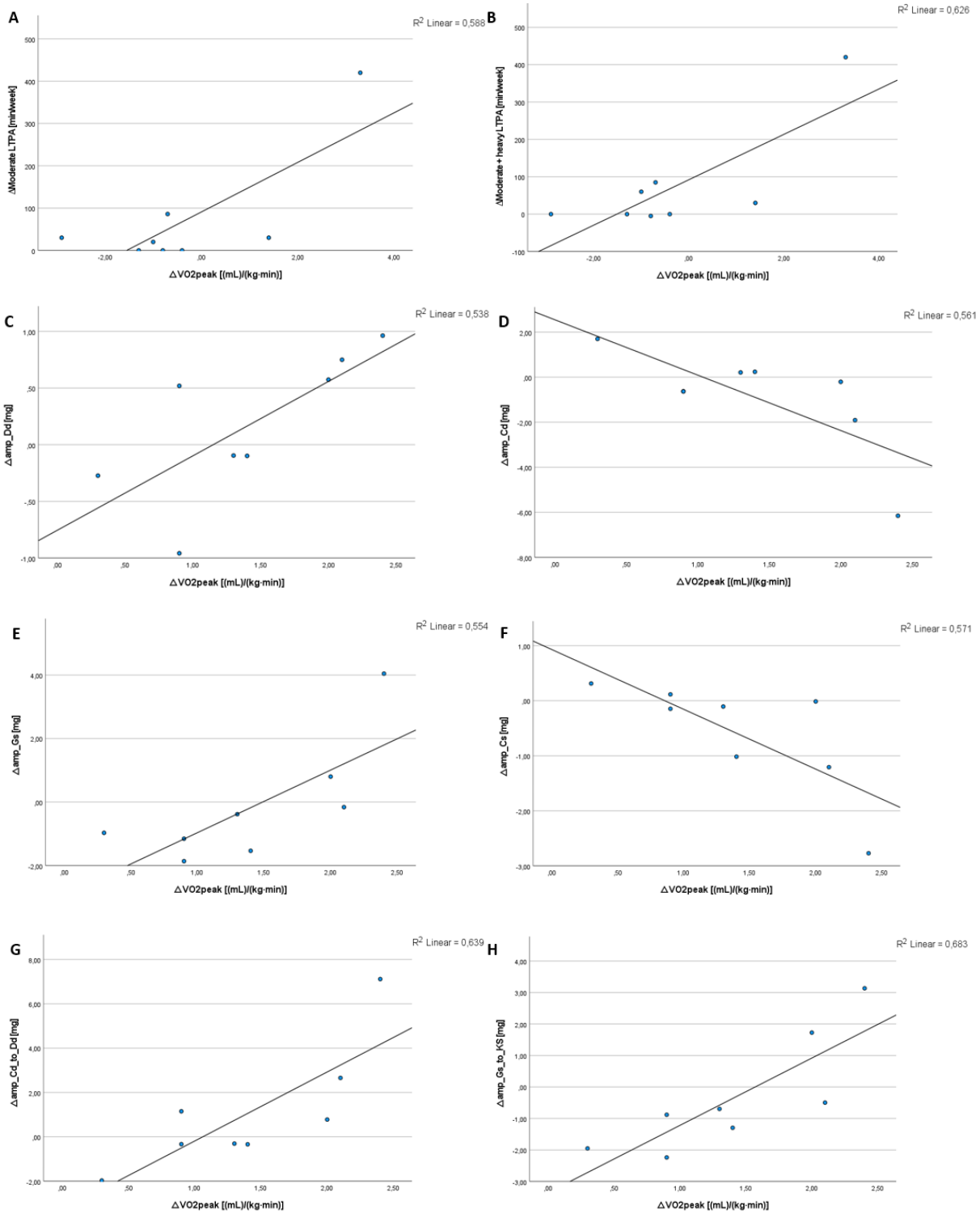
*Table 7: Pearson's correlation (R) between the change (△) in VO_{2peak} and the change (△) in SCG measurements, from BL to 6W. Significant changes is indicated with bold and " * ".*

	Total		Control		Træning	
	$\triangle VO_{2peak}$ (n = 16)		$\triangle VO_{2peak}$ (n = 8)		$\triangle VO_{2peak}$ (n = 8)	
	Pearson Correlation	p-value	Pearson Correlation	p-value	Pearson Correlation	p-value
$\triangle VO_{2peak}$	1.000		1.000		1.000	
△amp_Dd	.086	.751	-.312	.452	**.734***	.038
△amp_Cd	-.366	.163	-.316	.446	**-.749***	.033
△amp_Ed	.279	.295	-.239	.568	.631	.094
△amp_Fd	.240	.370	.431	.286	-.349	.396
△amp_Gs	.123	.651	.272	.515	**.744***	.034
△amp_Fs	-.136	.616	-.320	.440	-.006	.989
△amp_KS	.130	.631	.027	.949	-.184	.662
△amp_Ls	-.065	.812	.176	.677	-.200	.635
△amp_Bd	.129	.633	-.172	.684	.017	.968
△amp_Ds	.272	.308	.596	.119	.215	.608
△amp_Cs	-.287	.281	.183	.664	**-.756***	.030
△amp_Cd_to_Dd	.330	.212	.101	.811	**.799***	.017
△amp_Fs_to_Gs	.152	.573	.302	.468	.630	.094
△amp_Gs_to_KS	.044	.872	.168	.691	**.826***	.011
△amp_Ls_to_KS	-.104	.701	.064	.881	-.075	.861
△amp_Dd_to_Ed	-.220	.413	.023	.958	-.346	.401
△amp_Fd_to_Ed	-.152	.574	.358	.385	-.631	.093
△amp_Cd_to_Ed	-.373	.155	-.099	.815	**-,722***	.043

*** Correlation is significant at the .05 level**

△ change from baseline to 6 week follow-up

Signifikant correlations from Table 6, and Table 7 are illustrated in Figure 5.


A
R² Linear = 0,588
ΔModerate LTPA [min/week]
ΔVO2peak [(mL)/(kg·min)]
B
R² Linear = 0,626
ΔModerate + heavy LTPA [min/week]
ΔVO2peak [(mL)/(kg·min)]
C
R² Linear = 0,538
Δamp_Dd [mg]
ΔVO2peak [(mL)/(kg·min)]
D
R² Linear = 0,561
Δamp_Cd [mg]
ΔVO2peak [(mL)/(kg·min)]
E
R² Linear = 0,554
Δamp_Gs [mg]
ΔVO2peak [(mL)/(kg·min)]
F
R² Linear = 0,571
Δamp_Cs [mg]
ΔVO2peak [(mL)/(kg·min)]
G
R² Linear = 0,639
Δamp_Cd_to_Dd [mg]
ΔVO2peak [(mL)/(kg·min)]
H
R² Linear = 0,683
Δamp_Gs_to_KS [mg]
ΔVO2peak [(mL)/(kg·min)]

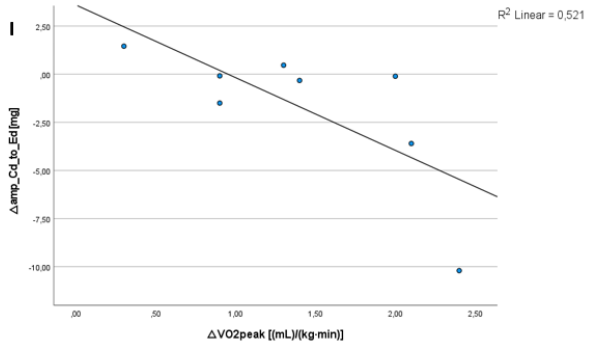


*Figure 5: Depictions of significant correlations from Table 6 and Table 7. The x-axis represent △VO2peak [(mL)/(kg·min)] and the y-axis **A** - **B** = △LTPA, and **C** - **I** = △SCG [mg]. All figures are presented with the best line of fit and R^2.*

Discussion

In part 1, this study investigated the possibility of developing a SCI-NEPE, based on data typically measured during routine clinical health checks, as well as SCG measurements. Then SCI-NEPEs were compared to AB-NEPEs. It was hypothesized that the SCI-NEPEs would outperform AB-NEPEs, in the SCI cohort investigated. The main findings were seven possible SCI-NEPEs, which could predict VO_{2peak}, shown in Figure 4. All SCI-NEPEs outperformed the AB-NEPEs, as seen in Table 3 and Table 5. SCI-NEPE-M7, was the SCI-NEPE with most included variables and highest predictive ability (R = .992; SEE = .968 $mL \cdot kg^{-1} \cdot min^{-1}$).

In part 2, the ability of the SCI-NEPEs to predict training-induced changes in VO_{2peak}, were examined on data from 6W. The SCI-NEPE-M3 had the highest correlation and lowest SEE (R = .787; SEE = 4.0 $mL \cdot kg^{-1} \cdot min^{-}$). SCI-NEPE-M5 had the highest PDOC (PDOC = 57%). Additionally, ΔVO_{2peak} was tested for correlation to all ∆values for the measured continuous variables, as depicted in Table 6 and Table 7. The parameters ∆amp_Dd, ∆amp_Cd, ∆amp_Gs, ∆amp_Cs, ∆amp_Cd_to_Dd, ∆amp_Gs_to_KS, and ∆amp_Cd_to_Ed were all correlated with ΔVO_{2peak} ($p < .05$), exclusively in the training group.

Part 1

Variables included in the developed models

In SCI-NEPE-M1 - SCI-NEPE-M7, amp_Fd_to_Ed, hip-circumference, lesion-level, RHR, amp_Ls, amp_Bd and height were included hierarchically in the seven models, as seen in

Figure 4. The first measurement included was amp_Fd_to_Ed, defined as the difference between the amplitude of Fd and Ed, which is related to mitral valve opening (Mounsey, 1957; Sørensen et al., 2018). Early transmitral filling velocity (E-wave), is a measure of peak velocity flow through the mitral valve, in the early diastole. E-wave has been shown to be higher in AB trained athletes, as well as after eight weeks of training in individuals with SCI (Gibbons et al., 2016; Hashimoto and Okamoto, 2020; Moro et al., 2013; Zhu et al., 2014). Remodelling of an athlete's heart causes increased negative-pressure in the LV in the early diastole, because of enlarged LV diameter. Increased negative-pressure causes vigorous suction of the blood, through the mitral valve in the beginning of its opening (Levine, 2008; Yellin et al., 1990). This is an important component for augmented cardiac output, as there is less time for ventricular filling during high HR (Levine, 2008). Thus it is plausible that amp_Fd_to_Ed is a measure of greater acceleration caused by the initial outward forces of greater transmitral suction effect and early ventricular filling (Levine, 2008; Mounsey, 1957; Sørensen et al., 2018).

Hip circumference and height are both measures that are represented in SCI-NEPEs and are related to body composition and size (Sharma et al., 2017, 2013). Height is normally factored into most AB-NEPEs by BMI, and people with greater height usually have greater absolute VO_{2peak} because they tend to have bigger lungs and greater cardiac output due to bigger hearts (Evans et al., 2017; Siahkouhian, 2009). VO_{2peak} is negatively correlated with %body fat, and positively correlated with fat free mass (Rump et al., 2002; Sharma et al., 2017, 2013). Hip circumference is a proxy measure of body fat (Wang and Hoy, 2004), which is a possible explanation as to why hip circumference is included in some of the SCI-NEPEs.

SCI injury-level was also included in SCI-NEPE-M3 - SCI-NEPE-M7, and is a measure with high effects in the models (β-coefficient 5.182 - 8.438). In general, higher lesion-level increases the disability-level, lowers HR, and increases likelihood of sedentary lifestyle (Myers et al., 2007; Taylor, 2016). Thus, individuals with a high lesion-level usually have decreased VO_{2peak}, compared to those with low injury-level (Myers et al., 2007). This measurement could have been implemented in many forms into the SCI-NEPEs, which might have been more accurate, e.g. implementing more intervals, or implementing a score for incomplete or complete injuries e.g. AIS. The small sample-size in the present study prevents a high division in categorical variables (Ogundimu et al., 2016).

Another parameter present in some of the SCI-NEPEs is RHR, which is a measure often used in NEPEs (Peterman et al., 2020). RHR is lower in well-trained individuals, as heart size and EDV increases, thereby increasing the potential for high cardiac output at high HR (Reimers et al., 2018).

The SCG measurements; amp_Bd and amp_Ls, are included in some of the SCI-NEPEs, as seen in Figure 4. amp_Bd is suggested to be related to aortic valve closure (Sørensen et al., 2018). When the aortic valve closes, the heart is accelerated towards its apex (Mounsey, 1957; Sørensen et al., 2018). amp_Cd_to_Dd, also suggested to be related with aortic valve closure, has the greatest correlation to VO_{2peak} in AB (Sørensen et al., 2020). amp_Bd and amp_Cd_to_Dd are closely related. amp_Bd most likely constitutes the closure event of the aortic valve (AV), while amp_Cd_to_Dd corresponds to the deflection caused by the closing. Thus it is difficult to interpret how cardiac function is affected by fluctuations in amp_Bd. amp_Ls is presumably related to the maximum ejection phase, caused by ventricular contraction (Mounsey, 1957; Sørensen et al., 2018). EDV and LV-mass changes with training, and results in larger CO (Levine, 2008; Zilinski Jodi L. et al., 2015). It would make sense that a larger deflection in amp_Ls, could reflect a more forceful ejection caused by adaptations to EDV and LV-mass. In contrast the relationship between VO_{2peak} and amp_Ls found in present study is inverse (negative β-coefficient, as seen in Figure 4). A negative β-coefficient is surprising, given that a faster upward acceleration in the heart possibly reflects more powerful contraction. Thus amp_Ls as a model parameter might be a spurious find.

Variables not included

Now the variables included in the SCI-NEPEs have been discussed. BMI and LTPA are commonly included variables in AB-NEPEs (Peterman et al., 2020). Hence, we will now consider possible explanations as to why these variables were not included. A plausible explanation for why weight and/or BMI did not significantly explain any variance in VO_{2peak}, and thus were not included in any of the SCI-NEPEs, is because it is already accounted for when VO_{2peak} is expressed relative to body mass [$mL \cdot kg^{-1} \cdot min^{-1}$]. Thus it is possible that the information from this variable is redundant.

Self-reported LTPA is, according to the review by Peterman et al. (2020), a measurement that typically improves the precision of NEPEs. In the present study, LTPA was not included in any of the models. This could be due to differences in what each person perceives as no activity, mild, moderate, and heavy LTPA (Ma et al., 2020; Martins et al., 2017), difference in explanation of the questionnaire, or simply because of coincidences. Such coincidences could be, if a person did more, or less LPTA, than they used to in the given week, e.g., one participant cleaned a house, resulting in 12 hours of mild exercise every day for a week.

Part 2

Six week follow-up and prediction of direction of change due to training

After a six week training period, the SCI-NEPEs, developed on BL-data, were tested to see how well SCI-NEPEs could predict the possible changes in VO_{2peak}. The only measure that is significantly different from BL to 6W is VO_{2peak}, in the training group ($p < .05$), as seen in Table 4A. As seen in Table 3 and Table 5, SCI-NEPE-M6 and SCI-NEPE-M7 perform very poorly at 6W (R = .608 - .606), compared to BL (BL: R = .983 - .992; 6W). This suggests that the SCI-NEPEs were overfitted to the cohort (Hawkins, 2004). SCI-NEPE-M3 and SCI-NEPE-M5 performed the best at 6W, with SCI-NEPE-M3 having the smallest %SEE, and SCI-NEPE-M5 having the best PDOC, as seen in Table 5. This suggests that the simpler SCI-NEPEs are less overfitted, and more viable for general use in the SCI-population (Hawkins, 2004). None of the SCI-NEPEs could predict the direction of change in VO_{2peak}, in the training group, very well. SCI-NEPE-M5 performed the best with 57% correct PDOC, which is typical for a NEPE (Peterman et al., 2020), and consistent with the results reported by Sørensen et al.'s (2020) (58.8%). The fact that SCI-NEPE-M5 has a PDOC of 57%, could be because none of the parameters included in the SCI-NEPEs, correlated with changes in the VO_{2peak}, as seen in Figure 4, and Table 6 and 7. Only changes in LTPA, and seven SCG measurements, correlated with ΔVO_{2peak}, as seen in Table 6 and 7. The NEPE from Sørensen et al. (2020) has a low R (.166) and a high SEE (13.1), when used on the individuals with SCI, in the present study, but it had 100% correct PDOC in the training group, as seen in Table 5. This could be because Sørensen et al.'s (2020) NEPE contains the amp_Cd_to_Dd, which is one of the SCG measurements that correlates with changes in VO_{2peak} (as well as amp_Cd and amp_Dd individually), as seen in Table 7. It has been suggested that a higher amp_Cd_to_Dd, is connected to a faster ventricular relaxation, and increased diastolic filling, which in turn increases stroke volume, and cardiac output (Sørensen et al., 2020). amp_Cd_to_Ed, could also be related to the deflection from aortic valve closure, and it is likely the same cardiac changes and/or events as amp_Cd_to_Dd that causes this measure to change as well.

Changes in amp_Gs_to_KS, and amp_Gs also correlated with ΔVO_{2peak} in the present study, as seen in Table 7. amp_Gs is suggested to be related to aortic valve opening (Sørensen et al., 2018). The difference in acceleration expressed as amp_Gs_to_KS, is probably due to blood being pumped out into the aorta (Sørensen et al., 2018). A greater amp_Gs_to_KS could be related to increased LV-mass, or increased EDV, which in turn increases cardiac

output (Gibbons et al., 2016). Both LV-mass and EDV, has been shown to increase in individuals with SCI, after eight weeks of functional electrical stimulation assisted rowing training (Gibbons et al., 2016), thus it is a plausible theory.

Changes in amp_Cs are negatively correlated to changes in VO_{2peak}. amp_Cs is related to peak atrial inflow (Sørensen et al., 2018). It is possible that an increase in left atrial volume, would correspond to a greater negative pressure, and thus suck the blood faster into the left atrium, which would give a higher negative amplitude in the SCG signal, as the heart accelerates downwards (Levine, 2008; Sørensen et al., 2018). According to Mahjoub et al. (2019), six weeks of training resulted in significantly ($p < .05$) increased left atrial (LA) volume. Six weeks is the same training period as in present study, making the theory plausible, even though the study by Mahjoub et al. (2019) was on AB.

∆Moderate LTPA and ∆moderate + heavy LTPA, was positively correlated with ΔVO_{2peak}, in the control group, depicted in Table 6. A participant took part in a study concurrently with the present study, with a different training intervention. The participant had a change in moderate LTPA and moderate + heavy LTPA of 420 minutes/week from BL to 6W, and had the highest $\Delta VO2_{peak}$ (3.3 $mL \cdot kg^{-1} \cdot min^{-1}$) of all participants regardless of group, as seen on Figure 5A and Figure 5B. Thus this could be part of the reason why there was a correlation between $\Delta VO2_{peak}$ and ∆moderate LTPA and ∆moderate + heavy LTPA, in the control group. If this participant is removed as an outlier, there is no significant correlation between ΔVO_{2peak} and ∆moderate LTPA and ∆moderate + heavy LTPA.

Limitations and future perspectives

The present study has only tested parameters that are possible to measure at a standard clinical visit (although for measuring SCG, there needs to be an accelerometer, with automated algorithm present), which makes it possible for clinical personnel to estimate CRF in individuals with SCI, during yearly check-ups, using the SCI-NEPEs suggested in present study. Due to the pandemic “COVID-19”, it was not possible to validate the SCI-NEPEs developed in present study on a different cohort, because of restrictions at University of Aalborg. When the opportunity for collecting new data is available, we recommend including a larger cohort. We would then suggest to validate the model on another cohort, eg. via cross-validation, before applying the developed SCI-NEPEs in a clinical setting. Although studies investigating individuals with SCI typically have a small sample-size (Bernard et al., 2000; Gibbons et al., 2016), as it is a small population, hence this might be difficult.

Furthermore, it is important to deeper investigate the role of SCG in SCI-NEPEs, as the results obtained in the present study suggest there may be significant advantages of using SCG in SCI-NEPEs, for a more precise estimate of CRF. To our knowledge no studies have investigated training induced changes in SCG parameters. Thus the significant correlations between ΔVO_{2peak} and Δamp_Dd, Δamp_Cd, Δamp_Gs, Δamp_Cs, Δamp_Cd_to_Dd, Δamp__Gs_to_KS, and Δamp_Cd_to_Ed, as seen in Table 7, are results that all needs to be further investigated, as predictors in SCI-NEPEs. This is because SCG measurements possibly correspond to physiological and anatomical changes, which is important for CRF (Sørensen et al., 2018).

In this present study, the prediction of changes in VO_{2peak}, is based on a six week training period. We recommend investigating a longer training period, as there are different myocardial adaptations to six weeks compared to three-, six-, nine months, and one year of training (Arbab-Zadeh et al., 2014; Mahjoub et al., 2019), and therefore it would be interesting to see how SCG-parameters change due to a longer training period, preferably with a larger cohort.

In the present study there has been a heightened focus on adaptations in the heart, and the effects on VO_{2peak}. Although these are not the only factors affecting change in VO_{2peak}, after a training period. When measuring VO_{2peak} by arm-crank ergometer, peripheral factors such as lactate threshold (Larsen et al., 2016) and muscular adaptations such as mitochondrial size and number (Holloszy), and increased capillarization (Gliemann, 2016), can play a key role in the measured VO_{2peak}. Especially considering arm-crank as VO_{2peak} test modality, where not much relative muscle mass is used, compared to eg. running. Hence, peripheral factors, rather than central factors, possibly limits performance (Larsen et al., 2016).

Conclusion

In part one, we developed SCI-NEPEs that vastly outperformed all compared AB-NEPEs in predicting VO_{2peak}. In part two, the SCI-NEPEs predictive accuracy fell at 6W compared to BL, but still vastly outperformed all compared AB-NEPEs. The more complex SCI-NEPEs were possibly prone to overfitting, and all the SCI-NEPEs need to be validated before being used in a clinical setting.
Additionally, changes in seven SCG measurements that were not part of the developed SCI-NEPEs, were found to correlate with ΔVO_{2peak} and warrants further investigation, when considering development of SCI-NEPEs, and when investigating SCG in relation to VO_{2peak}. .

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