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New insights into cardiorespiratory function in health and disability

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1. Summary

Cardiovascular disease is the leading cause of mortality in developed countries. Certain risk factors (i.e. overweight, type II diabetes) are preventable and treatable through, for instance, physical activity. To estimate long-term training adaptations, it is time and cost efficient to examine the effectiveness of an acute training stimulus. Therefore, the aim of this work was to provide new insight into cardiorespiratory function in response to training modes that are relevant to cardiovascular health and performance.

Studies involving training of respiratory muscles suggest a beneficial effect on exercise performance. However, the results remain controversial because some studies have failed to show functional improvements in exercise performance. A determinant factor for an effective training stimulus might represent the lung volume at which respiratory efforts are performed.

Therefore, we investigated the extent to which respiratory muscle fatigue is associated with lung volume during inspiratory loaded breathing (ILB) in twelve healthy individuals. Lung volumes were estimated by use of optoelectronic plethysmography. We found that after ILB, six subjects significantly decreased maximal inspiratory pressure (-16 ± 10%), while the other six subjects did not (0 ± 7%). Only subjects with decreased respiratory muscle strength lowered end-expiratory rib cage volume (volume at which inspiration is started) below resting values during ILB. These results suggest, that respiratory muscle fatigue depends on the lung volume from which inspiratory efforts are initiated during ILB.

In contrast to ILB, the most straightforward way to improve cardiovascular health is through exercise modes involving large muscle groups (i.e. cycling). However, for individuals with

muscle paralysis, such as cervical spinal cord injury (cSCI), this is not applicable, thus cSCI commonly exhibit low levels of cardiorespiratory fitness. Therefore, effective cardiorespiratory training modes and measurement systems to reliably estimate cardiac function are of particular interest in this population.

The Innocor^{TM} system allows non-invasive cardiac output determination. However, reliability of this technology may be compromised in cSCI due to the altered autonomic nervous system and reduced lung function. Therefore, we assessed the reliability at rest and during exercise in cSCI and compared it to pair-matched able-bodied individuals (AB). We found acceptable reliability of cardiac output measurements at rest and during exercise using Innocor^{TM} in cSCI, and it was was comparable to that found in AB.

Next, we aimed to determine whether arm-crank or wheelchair exercise has the greater potential to improve cardiorespiratory fitness in cSCI. We measured cardiorespiratory responses to exercise in cSCI and compared these to pair-matched AB. We found that cardiorespiratory responses to exercise were similar between the two exercise modes in cSCI and AB. However, cardiac output was lower in the cSCI compared to AB at identical workloads, mainly resulting from the inability of cSCI to increase stroke volume. This failure to increase stroke volume most likely results from impaired venous return related to an inefficient vasoconstrictor response in non-working muscles. Consequently, more effective training modes should be considered to ultimately enhance cardiovascular health in cSCI.

In conclusion, the present investigations on different training stimuli show important aspects to be considered to improve training concepts in health and disability.

2. Zusammenfassung

Kardiovaskuläre Erkrankungen gehören zu den häufigsten Todesursachen in der westlichen Bevölkerung. Einige der Risikofaktoren (z.B. Übergewicht, Typ II Diabetes) können durch körperliches Training verhindert oder vermindert werden. Um die Effektivität einer Trainingsintervention abzuschätzen, ist es sinnvoll und effizient, die Auswirkungen eines einzelnen Trainingsreizes zu untersuchen. Das Ziel dieser Arbeit ist daher, die Erkenntnisse hinsichtlich neuer Trainingsmodalitäten für Gesunde und körperlich Behinderte zu erweitern.

Zahlreiche Studien zeigen, dass ein Training der Atmungsmuskulatur die Leistungsfähigkeit verbessern kann, wobei einige Studien diesen Effekt nicht nachweisen konnten. Möglicherweise beeinflusst das Lungenvolumen während des Trainings die Effektivität dieser Trainingsart, ein Faktor, dem bis anhin wenig Beachtung geschenkt wurde.

Deshalb untersuchten wir den Zusammenhang von Atmungsmuskelermüdung und Lungenvolumen während inspiratorischem Widerstandsatmen. Während das Widerstandsatmen die Atmungsmuskelkraft bei einer Gruppe von sechs Probanden (A) reduzierte (-16 ± 10%), blieb sie bei den restlichen sechs (B) unverändert (0 ± 7%). Es zeigte sich, dass nur die Gruppe A die Einatmung bei einem Volumen unterhalb des Ruhewertes startete. Dass heisst, dass die Atmungsmuskelermüdung abhängig ist vom Lungenvolumen, bei dem das Widerstandsatmen durchgeführt wird, was entsprechend wichtige Konsequenzen für das Training der Atmungsmuskulatur hat.

Die optimalste Weise die Fitness zu verbessern ist jedoch, wenn möglich, ein Ganzkörpertraining. Allerdings ist diese Art von Training für Menschen mir zervikaler

Querschnittlähmung (zQL) aufgrund der extensiven Muskellähmung nicht möglich, was häufig eine Reduktion der kardiorespiratorischen Fitness zur Folge hat. Effektive Trainingsmodalitäten und entsprechende Messmethoden, um die kardiovaskuläre Fitness zu testen, sind deshalb von wichtiger Bedeutung für diese Personengruppe.

Ein neuartiges System (Innocor^{TM}) erlaubt die nicht-invasive Bestimmung des Herzminutenvolumens nebst anderer Parameter. Allerdings könnte die Reliabilität dieses Messsystems bei zQL als Folge veränderter autonomer Regulation und reduzierter Lungenfunktion kompromittiert sein. Unsere Untersuchung zeigte jedoch, dass das System auch bei zQL reliabel ist und dass die Reliabilität im Rahmen derer von Fussgängern liegt.

Mittels Innocor^{TM} untersuchten wir daher, ob sich Armkurbeln oder Rollstuhlfahren besser eignet, um die kardiorespiratorische Fitness von zQL zu verbesseren. Zu diesem Zweck bestimmten wir die maximalen kardiorespiratorischen Belastungen während diesen Aktivitäten in zQL und Fussgängern. Innerhalb der Gruppen unterschied sich die kardiorespiratorische Belastung nicht zwischen den beiden Modalitäten. Hingegen war das Herzminutenvolumen der zQL tiefer als dasjenige der Fussgänger bei gleicher Leistung, was hauptsächlich darauf beruhte, dass sich bei den zQL, das Schlagvolumen nicht erhöhte. Kleine Schlagvolumina bei zQL sind möglicherweise die Folge einer fehlenden sympathischen Vasokonstriktion in der nicht-arbeitenden Muskulatur. Es zeigt sich daher, dass auch maximale Armbelastungen bei zQL kaum zu einem Training des kardiovaskulären Systems führen und dass deshalb nach anderen Trainingsmodalitäten gesucht werden muss.

Zusammenfassend zeigt diese Arbeit neue, trainingsrelevante Aspekte, welche für die Optimierung von Trainingskonzepten von wichtiger Bedeutung sind.

3. General introduction

Adequate oxygen transport during exercise is essential to assure sufficient energy supply to the working muscles. The respiratory system (respiratory muscles, airways, lungs) and the cardiovascular system (blood, heart, blood vessels) transport the oxygen from the air to the exercising muscles.

In general, the respiratory system is not considered to restrict oxygen transport.[8] However, evidence exists that exercise induced respiratory muscle fatigue might compromise oxygen delivery to the exercising muscles by increasing sympathetic vasoconstrictor activity in working limb muscles.[30] In fact, several studies have demonstrated that respiratory muscle training improves exercise performance, while other studies did not find such an effect.[82,105]
In this context, part of the present work aims to explore determinants for effective respiratory muscle training and is focused on the association of respiratory muscle fatigue and the operating lung volume during increased ventilatory demands.

Besides the respiratory system, also the inability of the cardiovascular system to deliver sufficient oxygen to exercising muscles might affect exercise performance. A key factor within the cardiovascular oxygen transport system is the cardiac output (product of stroke volume and heart rate). The determinants of maximal cardiac output and its components are complex since metabolic, neural, humoral, and mechanical factors are involved.

Thus, in further parts of the present work, we aimed to investigate the importance of the sympathetic nervous activity on cardiovascular regulation during arm exercise by comparing the cardiac output response to exercise between individuals with cervical spinal cord injury

(cSCI) (disrupted sympathetic nerve pathways) to that of matched able-bodied indviduals (AB). Furthermore, to provide the basis for new training recommendations in cSCI, different types of arm-exercises were compared with respect to their potential to challenge the cardiorespiratory system.

Respiratory muscles

Muscles involved during breathing are the diaphragm (M. diaphragmaticus), rib cage muscles (RCM) (e.g. M. intercostales externus, M. intercostales internus, M. sternocleidomastoideus, Mm. scaleni), and abdominal muscles (e.g. M. rectus abdominis, M. transversus abdominis, M. obliquus externus abdominis, M. obliquus internus abdominis) (Figure 1).

Figure 1. Main muscles of respiration

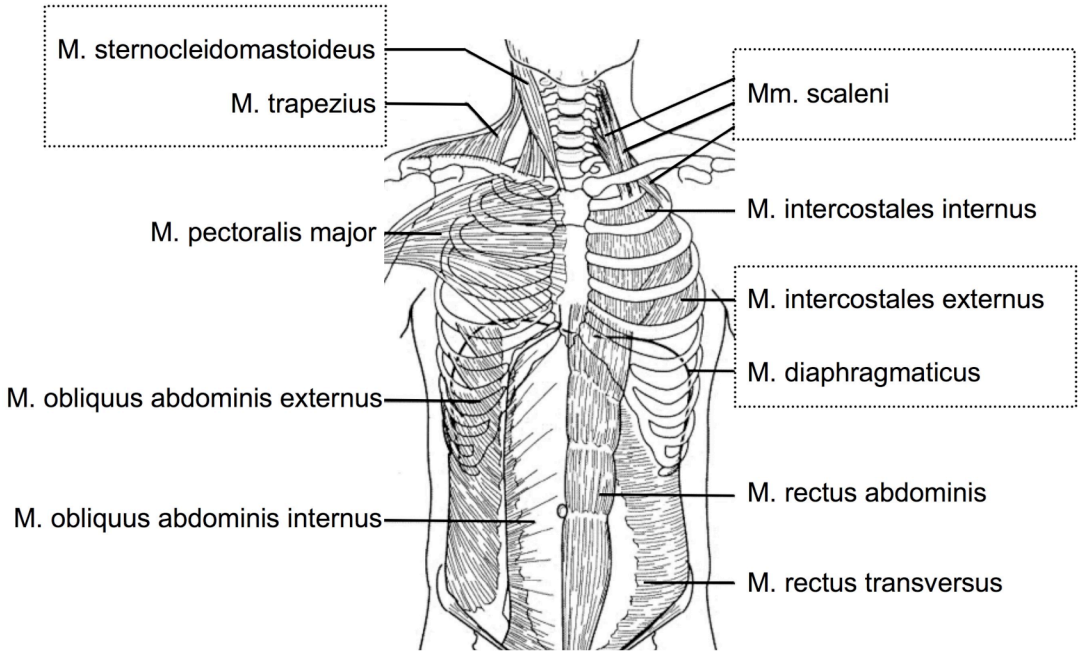

Illustration of the main muscles involved during breathing (modified from Winslow C. and Roszovsky J. (2003) *American Journal of Physical Medicine and Rehabilitation*). Muscles of inspiration are in boxes with dashed lines.

Inspiration is an active process that occurs when the inspiratory muscles contract, while expiration can be passive via elastic recoil of the lungs and the chest wall at rest. With increasing ventilatory demand, inspiratory and expiratory muscles are progressively recruited.[4,68] The diaphragm, acting piston-like,[120] has been described as being the main flow generator, in contrast to RCM and abdominal muscles which develop the pressure to displace the chest wall.[4] Accordingly, experiments showed that RCM could be selectively fatigued by pressure tasks while flow tasks mainly affected diaphragmatic performance.[55,83] Specific respiratory muscle training can improve respiratory muscles strength and / or endurance.[76,82]

Respiratory muscle training

Strength training (e.g. inspiratory loaded breathing (ILB)) is characterized by force tasks using external resistances or threshold pressure loads. Respiratory muscle endurance training (e.g. normocapnic hyperpnea (NH)) is characterized by flow tasks using mostly rebreathing systems to keep end-tidal CO_2 partial pressure constant. Improvements in exercise performance have been reported as a result of both types of training.[81,105,118] Nevertheless, these training modes remain a matter of controversy[82,105] because some studies failed to show functional improvements in exercise performance. A further point that contributes to this debate is the fact that the exact mechanism, by which respiratory muscle training improves whole body exercise performance is not yet completely understood.

Differences in training protocols might contribute to inconsistent findings. Training protocols that allow the prevention or minimize the development of respiratory muscle fatigue during a breathing task might not be effective.[73] For instance, since the recruitment of different muscle groups varies as a function of lung volume,[78,129] alterations in lung volume during e.g. ILB

might prevent the development of respiratory muscle fatigue thereby leading to an ineffective training stimulus.

Operating lung volumes and inspiratory loaded breathing (ILB)

Inspiratory muscle strength increases with decreasing lung volume.[2,12,26,113] Accordingly, it has been demonstrated that the highest maximal inspiratory pressure (MIP) is achieved after complete expiration, i.e. when inspiring from residual volume (RV). Several studies have provided evidence that the action of the inspiratory RCM determines maximal inspiratory pressure at RV, while the diaphragm is assumed to contribute less to pressure generation at RV.[2,55,83] In this context, prevention of RCM-fatigue by altering the operating lung volume during ILB would not provide an effective training stimulus to ultimately improve respiratory muscle strength.

Assessing operating lung volumes and breathing strategies during ILB, by use of optoelectronic plethysmography along with respiratory muscle strength measurements, may discover new determinants of respiratory muscle fatigue development. In the study presented in chapter 4, we hypothesized that dominance of the RCM- versus diaphragmatic-fatigue would depend on the lung volume at which inspiratory efforts are initiated and that RCM-fatigue would be associated with starting at lower lung volumes.

Spinal cord injury

In individuals with a high-level spinal cord injury, lung volume is compromised due to extensive muscle paralysis but other bodily functions are affected too, possibly contributing even more to exercise limitation.

Spinal cord injury leads to the loss of central motor command of the muscles innervated below the level of lesion. Motor-complete cervical spinal cord injury – transection between the first (C1) and the eighth vertebra (C8) – represents the most dramatic form of spinal cord injury. Individuals with motor-complete lesion of the spinal cord above C3 (above the level of phrenic motorneurons) commonly require assisted ventilation (e.g. mechanical ventilation, phrenic nerve pacing).[15] Lesions between C3 and C5 allow voluntary movement of the diaphragm and partially the triceps, while normal hand grip function is nearly absent. Manual wheelchair propulsion is, in general, not possible after a motor-complete spinal cord lesion above C5. Lesions between C5 and C8 allow all/most triceps functions, wrist flexion and extension with limited grasp and release function.[95] Individuals with motor-complete lesions at this level are commonly able to move around in a manual wheelchair, however, difficulties involving inclines or covering long distances compromise their independent locomotion.[46,92]

The extensive skeletal muscle paralysis in individuals with cervical spinal cord injury (cSCI) dramatically reduces their ability to perform exercise, and they commonly exhibit low levels of cardiorespiratory fitness.[48,67] Partly due to the low level of cardiorespiratory fitness, cardiovascular diseases have become one of the leading causes of mortality in chronic non-ventilated cSCI.[44,90] Regular physical activity has indeed the potential to decrease certain cardiovascular risk factors, e.g. insulin resistance, dyslipidaemia, vascular inflammation.[21] However, besides the small active muscle mass, the ability to perform exercise is also substantially affected by cardiovascular impairments.[62,95]

Autonomic dysfunction and cardiovascular control following cervical spinal cord injury

Interrupted sympathetic nervous pathways to the heart and low concentrations of circulating plasma catecholamines[28,72,104] reduce heart rate reserve and vasomotor regulation[74] during

exercise.[107] Owing to the absence of vasoconstriction in the non-exercising tissues, exercise hypotension[71] and inadequate blood redistribution[63,95,111] have been associated with venous blood pooling, which might in turn impair venous blood return and stroke volume in cSCI.[39,70] Sustained cardiac underloading results in cardiac atrophy, which is frequently observed in cSCI.[38,70,23,91]

Figure 2. Autonomic control of the cardiovascular and pulmonary systems

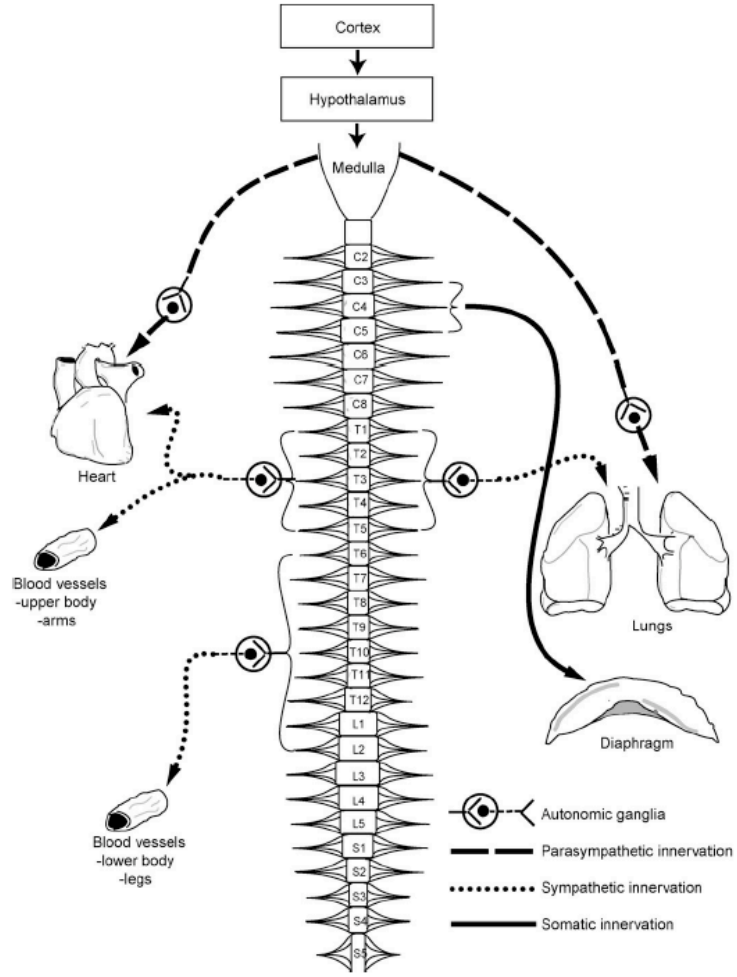

Illustration of the spinal cord and the autonomic innervation of the cardiovascular and pulmonary systems (from Krassioukov A. (2009) *Respiratory Physiology and Neurobiology*).

On this basis, investigations of exercise modalities with the potential to adequately volume load the heart are therefore of primary importance in cSCI. A promising approach is to use short bouts of intensive or maximal leg exercise training modes, which have been shown to improve stroke volume in able-bodied individuals (AB).[52] However, to date, it is not known, to what extent changes in cardiac output and stroke volume occur in response to maximal arm exercise in cSCI. Comparisons to AB are essential to distinguish whether the muscle mass involved during arm exercise might be *per se* too small to create an aerobic demand great enough to stress the central cardiovascular system[8,84] or whether a limitation might be specifically related to cSCI.

Therefore, knowing cardiac output and stroke volume changes in response to maximal exercise will improve the understanding of dynamics and limitations of the cardiovascular regulation in cSCI. Furthermore, this information may contribute towards optimizing training modalities and to verify training effects. A training mode with a large increase in stroke volume might have the highest potential to prevent cardiac atrophy, since the heart muscle adapts to overload stimuli.[9,39]

Determination of cardiac output and stroke volume

Gold standard methods to determine cardiac output are invasive and their use during maximal exercise is debated.[125] A non-invasive, valid and user-friendly method to determine cardiac output, is with the Innocor™ system (Innovsion, Odense, Denmark), which is based on inert gas rebreathing.[3] This technology estimates cardiac output by the rate of uptake of nitrous oxide that enters and leaves the bloodstream through the lungs. Stroke volume can be derived by simultaneous heart rate measurement. In the past, Innocor™ has been shown to provide reliable cardiac output measurements during maximal exercise in AB.[42]

Whether Innocor™ provides reliable cardiac output measurements in cSCI has not been investigated to date. This is important, because respiratory, cardiovascular, or neural impairments might affect the reliability of these measurements in this population. Reliability describes the amount of measurement error and is quantified by conventional reliability measures (e.g. intra- and interclass correlation coefficients, coefficients of variation, or limits of agreement).[6] Based on these measures, it can be decided whether Innocor™ is reliable enough for the intended purpose e.g. repetitive measurements within a day or over weeks. In addition, standard deviations obtained from repeated measurements provide the basis for sample size calculations needed for study planning.

Arm-crank *versus* wheelchair exercise

Arm-crank and wheelchair exercise are common training modes in cSCI. The two exercise modes differ, among other factors, in their propulsion ergonomics.[116] Less energy is required for the same workload during arm-cranking compared to wheelchair exercise.[20,47,56,112] Consequently, higher maximal workloads are achieved in response to incremental arm-crank compared to wheelchair exercise.[47,48,103,112] However, it is not known to what extent cardiac output and stroke volume change in response to these exercise modalities. Therefore, we aimed to determine the exercise type that evokes higher levels of cardiac output and stroke volume during maximal exercise. Short and maximal exercise bouts might be an interesting concept for cSCI since, in this population, extensive and long exercise duration are challenged by different factors, including high muscle fatigability, exercise hypotension, or postural discomfort.

In summary, the focus of this doctoral thesis was to gain a deeper understanding of cardiorespiratory function in response to different conditions by use of advanced technologies. Moreover, by pursuing an integrative approach, we aimed to provide relevant information related to exercise tolerance and to explore the effectiveness of different training impulses. This information is necessary to identify optimal training modalities and to enhance directly or indirectly cardiorespiratory fitness in AB and cSCI.

The main objectives of the present work were:

- To determine lung volume changes during ILB leading to predominant RCM- or diaphragmatic-fatigue in a group of healthy individuals.

- To establish test-retest reliability of cardiac output measurements by use of the Innocor^{TM} inert gas rebreathing method during arm exercise in cSCI.

- To evaluate exercise- and cSCI-specific limitations to cardiovascular regulation during maximal arm-crank and wheelchair exercise.

- To investigate physiological, mechanical, and psychological factors that are potentially relevant to exercise tolerance in cSCI.

4. Chest wall volume changes during inspiratory loaded breathing

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Introduction

Inspiratory loaded breathing (ILB) is a common training method to improve respiratory muscle strength. ILB involves high-resistance, low-speed contractions using external resistance or threshold pressure loads. The training effects of ILB on respiratory muscle function, physical performance, and perception of breathing have been extensively investigated in healthy subjects[82,105] and in pulmonary patients,[45] but findings remain controversial. Most studies show an increase in maximal inspiratory pressure (MIP) after ILB-training, some also demonstrate improvements in exercise capacity[37,85,99,123] while others fail to show any functional improvements during exercise.[49,128] The lack of functional improvement has been explained by learning effects, rather than structural and functional adaptations, being responsible for MIP-increases after ILB-training.[36,51,75,97]

Differences in training protocols might contribute to these inconsistent findings.[37,45] While details relating to training load, testing method, and ventilation are generally reported, most studies provide only few or no data on the range of lung volumes at which ILB was performed. It is recommended that subjects breathe over the entire lung capacity, i.e. from residual volume (RV) to total lung capacity (TLC). During home-based ILB, however, lung volumes are not controlled, and subjects might diverge from this instruction and adapt a breathing strategy to avoid respiratory muscle fatigue. In particular, starting inspiration at RV might be essential for effective respiratory strength training, since it is known that the strength of the rib cage muscles (RCM)[13,102] determines MIP (assessed at RV),[2,54,83] while the contribution of the diaphragm to MIP decreases towards RV.[13,54] Furthermore, it has been shown that the greatest improvements of MIP were achieved after performing ILB-training at

RV.[114] Hershenson *et al*.[33] showed that during ILB from RV, RCM fatigued preferentially, and they concluded that RCM are the main force generators during ILB.[83] Studies that did not control for lung volumes during ILB found either predominantly RCM- or diaphragm-fatigue developed.[35,98,119] This suggests that the diaphragm may also be involved during loaded breathing tasks. According to resistance training specificity,[88] preventing RCM from fatiguing, will most likely result in an insufficient training stimulus and fail to improve RCM-strength.

Therefore we aimed to assess the range of chest wall volumes (reflecting changes in lung volume) during ILB, carefully instructing subjects to breathe from RV to TLC prior to the breathing task, but there were no reminders during breathing, similar to home-based ILB. Accordingly, we wanted to investigate the influence of the range of chest wall volumes during ILB on changes in respiratory muscle strength, and to identify the ranges leading to preferential RCM- or diaphragm-fatigue. We assessed chest wall volume changes using optoelectronic plethysmography[16] (OEP; BTS Bioengineering, Milan, Italy) which allows volume changes of the chest wall to be partitioned into three compartments: the pulmonary rib cage, reflecting the activity of inspiratory and expiratory RCM; the abdominal rib cage, reflecting diaphragmatic activity; the abdomen, reflecting both diaphragm and abdominal muscle activity.[4] To assess fatigue, we compared MIP and maximal expiratory pressure (MEP), sniff nasal inspiratory pressure (SNIP), as well as breathing pattern during volitional normocapnic hyperpnea (NH) at an exercise-simulated target ventilation before and after 1h of ILB. Breathing pattern was used as an independent indicator of muscle fatigue, since rapid and shallow breathing is known to occur in the presence of fatigued[79] or weak[131] respiratory muscles and seems to be associated with RCM-fatigue.[119] We hypothesized that (i) the relative contribution of the pulmonary rib cage to tidal volume would decrease due to RCM-

fatigue during ILB, (ii) the dominance of RCM- (versus diaphragm)-fatigue would depend on the lung volume at which inspiratory efforts are initiated during ILB, and that RCM-fatigue would be associated with starting at lower lung volume.

Materials and methods

Subjects

Twelve healthy subjects (8 women, 4 men) with normal lung function were studied. After detailed information of the test procedures, subjects gave their written informed consent. The protocol was approved by the ethics committee of the ETH Zurich (EK2007-19) and performed according to the Declaration of Helsinki. Participants were required to refrain from strenuous physical activity for 48 h and from any physical activity the day before testing. Drinking caffeinated or alcoholic beverages on test days was forbidden and no food was allowed within the last 2 h before testing.

Study Protocol

Subjects reported to the laboratory on three separate occasions, separated by at least 48 h. Each subject was naïve to the loaded breathing protocol prior to the first session. During the first session, participants performed familiarization trials with the ILB and NH breathing devices and practiced lung function and respiratory muscle strength measurement maneuvers. The following two sessions were randomized. One session included the assessment of lung function, SNIP, MIP, MEP, 5 min of quiet breathing, 3 vital capacity maneuvers, 1 h of ILB, lung function, SNIP, MIP, and MEP measurement, concluded by 3 min of NH (NH_{after}). The other session consisted of 3 min of NH ($NH_{baseline}$). OEP-recordings were performed during ILB and NH.

Lung function and respiratory muscle strength

Lung function was assessed according to standard procedures[87] using a metabolic cart (Quark b^2, Cosmed, Rome, Italy). Baseline values were expressed as percent predicted using the prediction equations of Quanjer *et al*.[12] MIP (from RV), MEP (from TLC), and SNIP (from functional residual capacity; FRC) were assessed according to standard proceduresATS/ERS, [1] using the MicroRPM device (MicroMedical, Kent, UK). A minimum of five technically satisfactory measurements were conducted and the highest of three measurements with less than 5% variability difference was defined as the maximum.[126] Baseline values were expressed as percent predicted using the prediction equations of Wilson *et al.*[27] and Uldry and Fitting.[38]

Inspiratory loaded breathing

Subjects performed ILB while standing and were instructed to perform each breath from RV to TLC. During the test, no verbal encouragement was given. The initial target peak pressure was set at 80% MIP, which was reduced by 10 cm H_2O if the target could not be achieved for 10 - 20 s and it was increased again if possible, which was signaled by the subjects with a hand sign. Expiration was unloaded and breathing frequency was not imposed. Six subjects performed ILB using a threshold load device (Powerlung, Houston, USA). Loads were calibrated using a differential pressure transducer (DP45-30, Validyne Northridge, USA) according to the method of Wells *et al*.[3] Six subjects performed ILB using a resistive load device (MicroRMA, MicroMedical, Kent, UK). Subjects using the resistive load device were instructed to perform square wave pressures to produce a most similar time-pressure-pattern to that obtained during threshold loaded breathing. Visual feedback of the target pressure and the pressures achieved was given to the subjects.

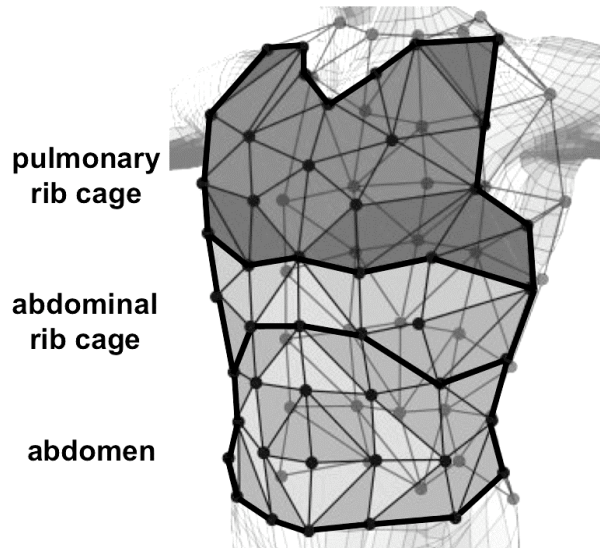
Normocapnic hyperpnea

Subjects performed NH using a partial rebreathing-system connected to the metabolic cart equipped with an infrared absorption sensor for CO_2-measurement to ensure normocapnia. Target minute ventilation was set at 70% of maximal voluntary ventilation, tidal volume and breathing frequency were not imposed. Subjects were verbally encouraged by the experimenter if minute ventilation dropped below the target.

Optoelectronic plethysmography

The volumes displaced by the three compartments of the chest wall during ILB and NH were measured using OEP[16] which records movements of 89 markers placed on the trunk of the subjects via 6 infrared cameras (Figure 1). The following parameters were derived from OEP-data; end-inspiratory and end-expiratory volumes (relative to average end-expiratory volume during quiet breathing), percentage contribution of the different compartments to tidal volume, tidal volume, breathing frequency, minute ventilation, mean inspiratory flow, and duty cycle.

Figure 1. Marker position and geometrical model (optoelectronic plethysmography)



Schematic diagram of the thoraco-abdominal surface triangulation (modified from www.btsbio engineering.com). The chest wall volume is modeled as the sum of the lung-apposed rib cage (pulmonary rib cage), diaphragm-apposed rib cage (abdominal rib cage) and abdomen (abdomen).

Data analysis

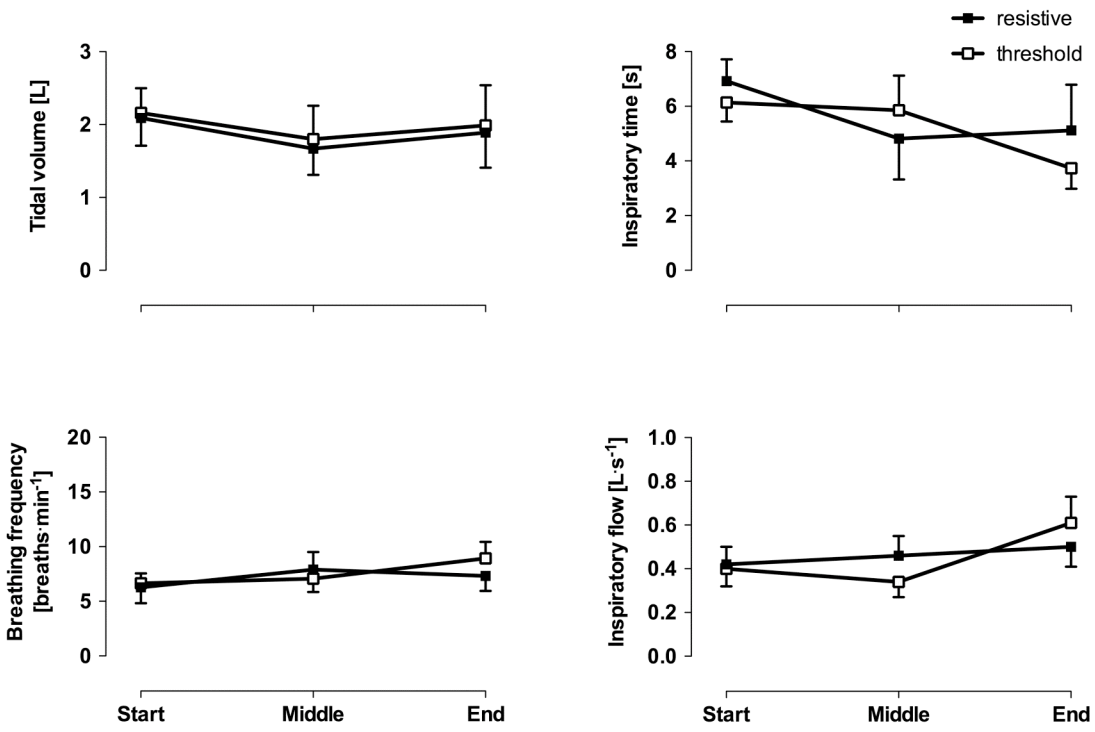
OEP data was averaged over 1 min of quiet breathing, the first 3 min (start), the middle 1 min (middle), the last 3 min (end) of ILB, and over 3 min of $NH_{baseline}$ and NH_{after}. To test for significant changes in the course of ILB, the Friedman test was applied. When significant, pairwise comparisons were performed using the Wilcoxon sign rank test. This test was also used for comparisons of data assessed before and after ILB. In addition, subjects were post-hoc divided into two groups. First, subjects were grouped according to the device (threshold versus resistive) used during ILB. Between-group comparisons of baseline values and within-group changes were performed using the Mann-Whitney U test. Since no significant difference was detected between groups (see results), subjects were stratified according to the change in MIP after ILB. During MIP assessments, values within 5% were considered as reproducible. Therefore we considered an MIP-change greater than 5% between assessments as a criterion for defining an MIP-decrease. Subjects with an MIP-decrease greater than 5% (n = 6) were assigned to group A (4 women, 2 men). Subjects with an MIP-decrease of less than or equal to 5% MIP (n = 6) were assigned to group B (4 women, 2 men). Comparisons between these two groups as well as between groups of different gender, were also performed with the Mann-Whitney U test. All results are expressed as mean ± standard deviation (SD), unless otherwise stated, and $p < 0.05$ was considered as statistically significant (SPSS 17.0, Chicago, IL, USA).

Results

Threshold versus resistive loading

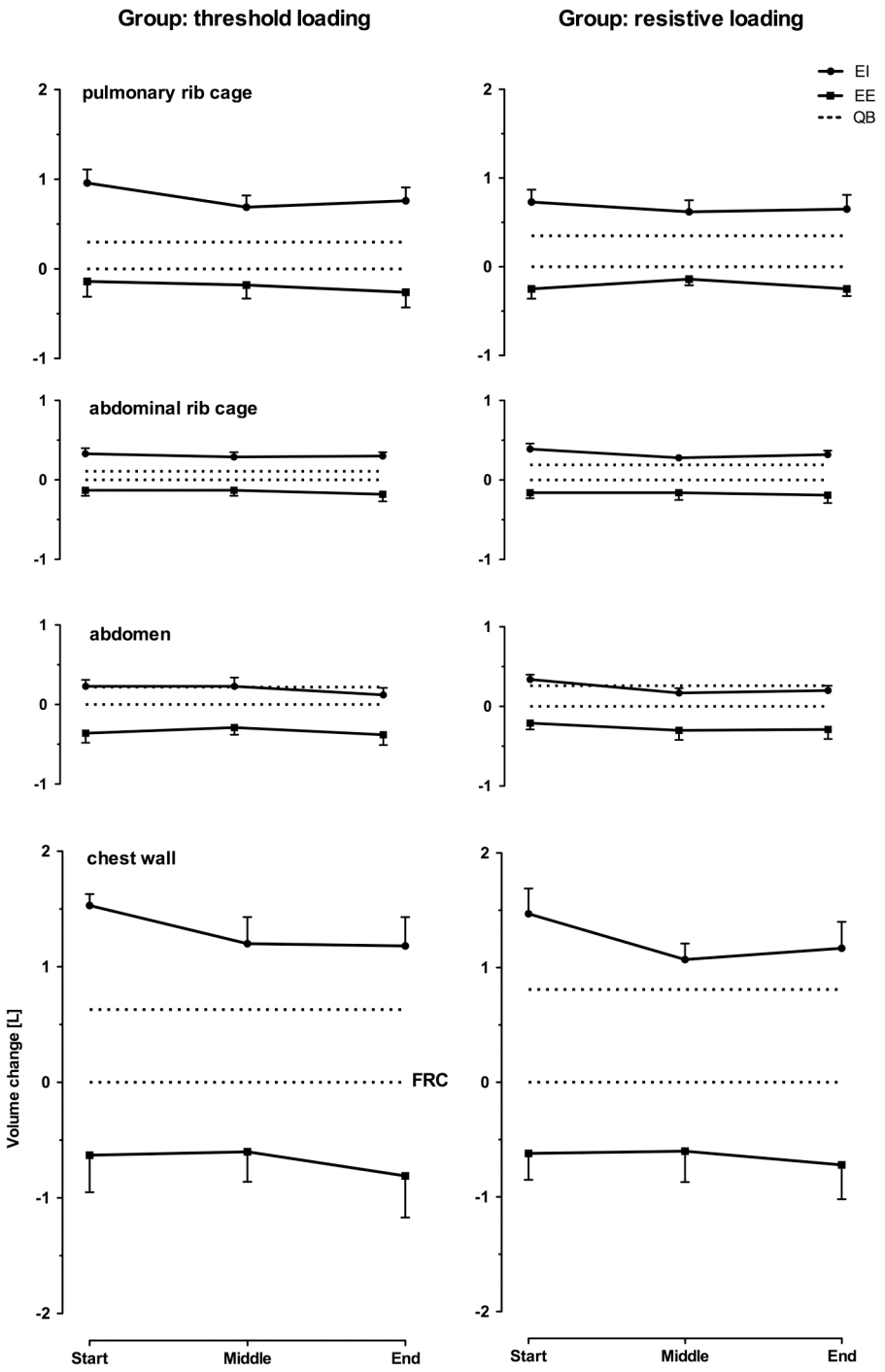
Mean peak pressures during ILB were not significantly different (p = 0.873) between the group using the threshold device (75 ± 7% MIP; 4 group A, 2 group B; 5 women, 1 men) and the group using the resistive device (76 ± 7% MIP; 2 group A, 4 group B; 3 women, 3 men). Changes of the chest wall compartments during ILB (Figure 3), the adherence to breathe over the entire vital capacity (threshold 45 ± 11 versus resistive 36 ± 14% VC) as well as mean tidal volume, breathing frequency, inspiratory flow, and inspiratory time, were not significantly different between groups using the different devices during ILB (Figure 2).

Figure 2. Breathing pattern in response to inspiratory threshold and resistive loaded breathing



Data is given as mean ± SE. Tidal volume, breathing frequency, inspiratory flow and inspiratory time during inspiratory loaded breathing, grouped by threshold (4 subjects group A, 2 subjects group B) and the resistive (2 subjects group A, 4 subjects group B) loaded breathing. No significant differences were found between the two groups.

Figure 3. Chest wall volume changes in response to inspiratory threshold and resistive loaded breathing



Data is given as mean ± standard error (SE). Changes in end-inspiratory (EI) and end-expiratory (EE) volumes, expressed relative to functional residual capacity (FRC) at the start, middle, and end of inspiratory loaded breathing. QB, quiet breathing. No significant differences were found between the two groups in the course of inspiratory loaded breathing.

Lung function and respiratory muscle strength

Anthropometric data, baseline lung function and respiratory muscle strength are shown in Table 1. Subjects in group A were significantly older than those in group B. Changes in MIP, MEP and SNIP did not correlate with age nor with the corresponding baseline values (both $p > 0.05$). Also, these changes did not differ significantly between female and male subjects (all $p > 0.05$). Average peak pressures during ILB were 77 ± 14 for group A and 74 ± 10% of MIP for group B ($p = 0.631$) with no significant change in the course of ILB. After ILB, MIP and peak expiratory flow were significantly reduced in group A, whereas forced inspiratory volume in 1 s and SNIP were significantly lower in group B (Table 2). Individual values of MIP and SNIP before and after ILB are shown in Figure 4.

Table 1. Subject characteristics, lung function, and respiratory muscle strength

	Group A	**Group B**	p - value
Age, yrs	32 ± 3	27 ± 2	0.010
Height, cm	169 ± 8	175 ± 9	0.335
Body mass, kg	64 ± 10	63 ± 9	0.749
FVC, % predicted	119 ± 13	115 ± 10	0.423
FEV_1, % predicted	112 ± 14	110 ± 11	0.262
PEF, % predicted	122 ± 17	106 ± 12	0.109
MVV, % predicted	133 ± 28	124 ± 19	0.262
MIP, % predicted	144 ± 30	119 ± 19	0.109
MEP, % predicted	142 ± 48	120 ± 37	0.337
SNIP, % predicted	79 ± 15	71 ± 23	0.602

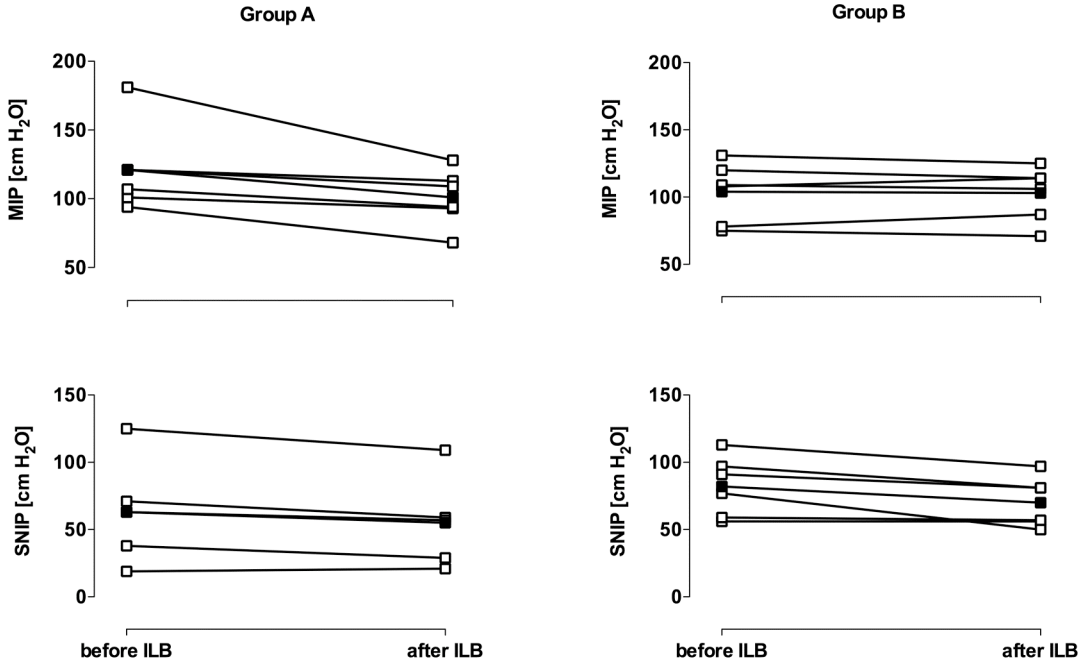
Data is given as mean ± SD. Group A (MIP decrease, 4 female, 2 male); Group B (no MIP decrease, 4 female, 2 male); FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; PEF, peak expiratory flow; MVV, maximal voluntary ventilation; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

Table 2. Lung function and respiratory muscle strength before and after inspiratory loaded breathing

	Group A		p - value	**Group B**		p - values	
	Before	After	Within group	Before	After	Within group	Δ
Lung function							
FVC, L	4.8 ± 0.6	4.8 ± 0.6	0.345	5.2 ± 1.2	5.0 ± 1.4	0.345	0.715
FEV_1, L	3.8 ± 0.5	3.8 ± 0.5	0.144	4.2 ± 0.8	4.2 ± 0.9	0.753	0.201
PEF, $L \cdot s^{-1}$	9.6 ± 1.9	9.5 ± 1.8	0.043	9.0 ± 2.5	9.0 ± 3.1	0.686	0.068
FIV_1, L	4.3 ± 0.7	4.1 ± 0.6	0.080	4.2 ± 0.8	3.9 ± 0.9	0.028	0.715
PIF, $L \cdot s^{-1}$	7.1 ± 1.9	6.5 ± 2.1	0.225	6.6 ± 1.7	6.3 ± 1.9	0.141	0.584
Respiratory muscle strength							
SNIP, cm H_2O	63 ± 40	55 ± 35	0.080	82 ± 22	70 ± 19	0.042	0.461
MEP, cm H_2O	157 ± 59	150 ± 41	0.311	141 ± 58	131 ± 60	0.080	0.631
MIP, cm H_2O	121 ± 31	101 ± 21	0.028	104 ± 28	103 ± 20	0.916	0.004

Data is given as mean ± SD. Group A (MIP decrease); Group B (no MIP decrease); FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; PEF, peak expiratory flow; FIV_1, forced inspiratory volume in 1s; PIF, peak inspiratory flow; SNIP, sniff nasal inspiratory pressure; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure. Δ = difference between within group changes (after minus before values).

Figure 4. Maximal inspiratory mouth pressure and sniff nasal inspiratory pressure before and after inspiratory loaded breathing



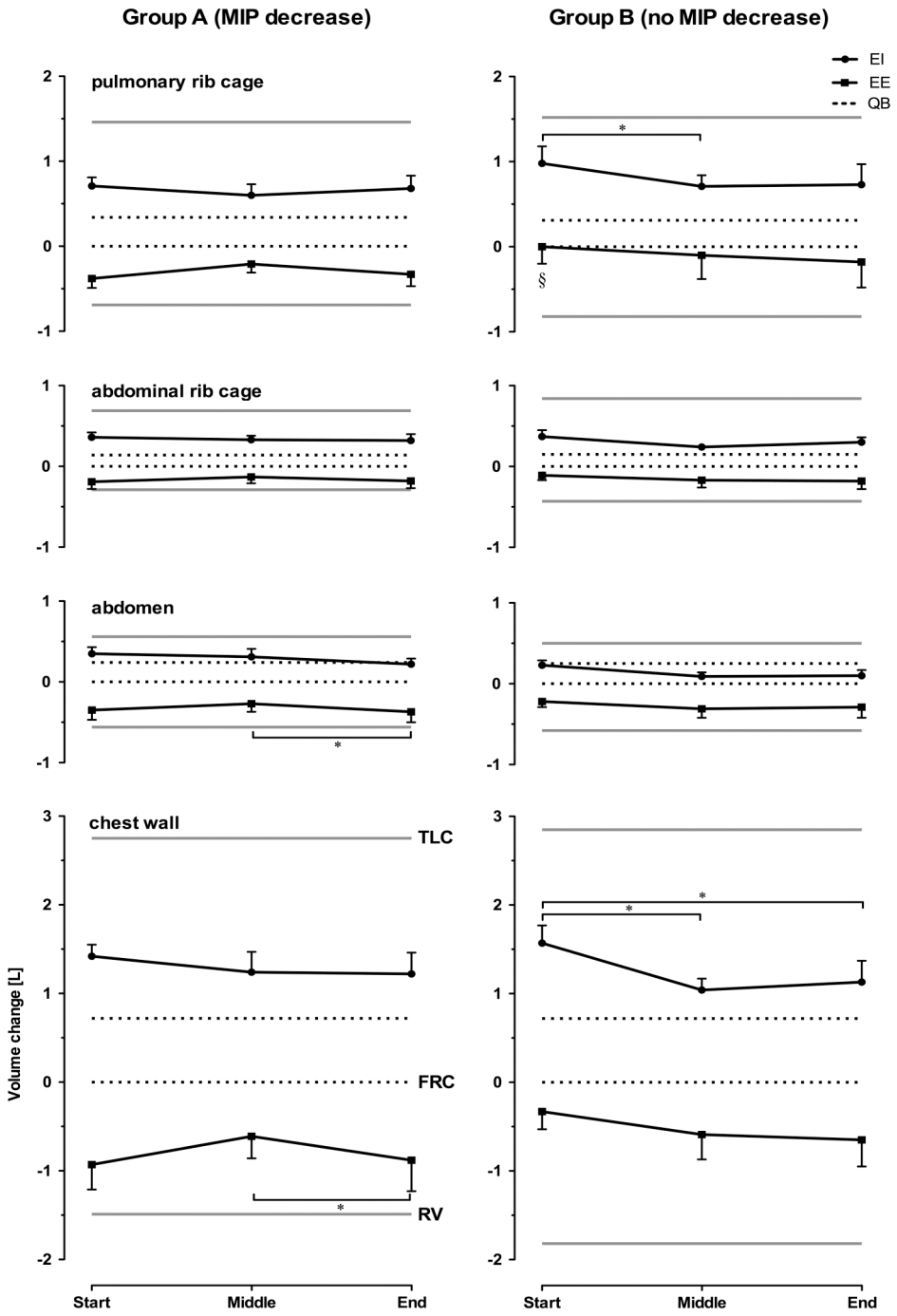
Individual values of maximal inspiratory mouth pressure (MIP) and sniff nasal inspiratory pressure (SNIP) before and after inspiratory loaded breathing for group A and group B. Means are represented by the black symbols.

Chest wall volumes and breathing pattern during ILB

At the start of ILB, the average contribution of the three chest wall compartments to tidal volume was not significantly different between group A (pulmonary rib cage: 48 ± 6, abdominal rib cage: 23 ± 2, abdomen: 29 ± 8%) and group B (pulmonary rib cage: 53 ± 10, abdominal rib cage: 25 ± 7, abdomen: 22 ± 5%). No significant changes were observed in the course of ILB. At the start of ILB, end-expiratory chest wall volume (EEV; beginning of inspiration) was significantly closer to RV in group A (15 ± 10% of vital capacity) than in group B (34 ± 15% of vital capacity, $p < 0.05$; Figure 5). During ILB, for group A EEV of the pulmonary rib cage remained significantly below FRC ($p < 0.01$). In contrast, EEV of the pulmonary rib cage was not significantly below FRC for group B ($p = 0.100$). During 1h of

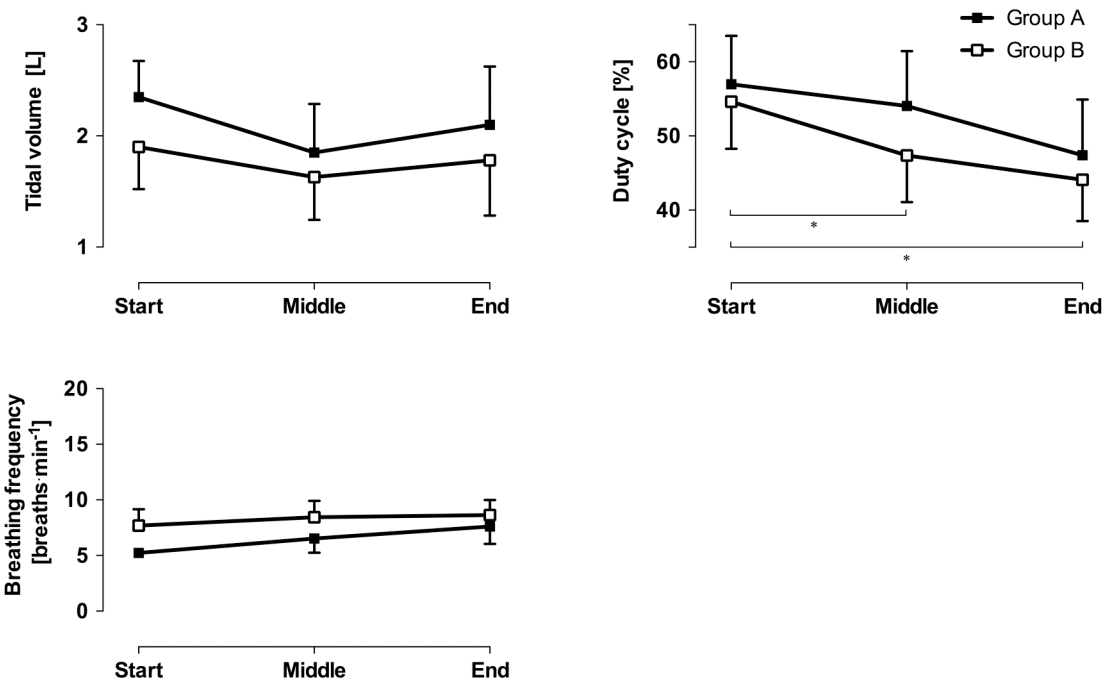
ILB, EEV of the chest wall tended to increase in group A subjects (0.32 ± 0.32 L, $p = 0.075$) after 30 min, and significantly decreased towards the end, resulting from a significant decrease in EEV of the abdomen. For group B, end-inspiratory volume (EIV) of the chest wall and pulmonary rib cage significantly decreased after 30 min, and no further changes were observed. Breathing pattern was not significantly different between the two groups (Figure 6).

Figure 5. Chest wall volume changes during inspiratory loaded breathing



Data is given as mean ± SE. Changes in end-inspiratory (EI) and end-expiratory (EE) volumes, expressed relative to functional residual capacity (FRC) at the start, middle, and end of inspiratory loaded breathing. Grey lines show maximal EI/EE volumes of the vital capacity. QB, quiet breathing; RV, residual volume; TLC, total lung capacity. * Significant difference within group ($p < 0.05$), and § for between group difference ($p < 0.05$).

Figure 6. Breathing pattern during inspiratory loaded breathing

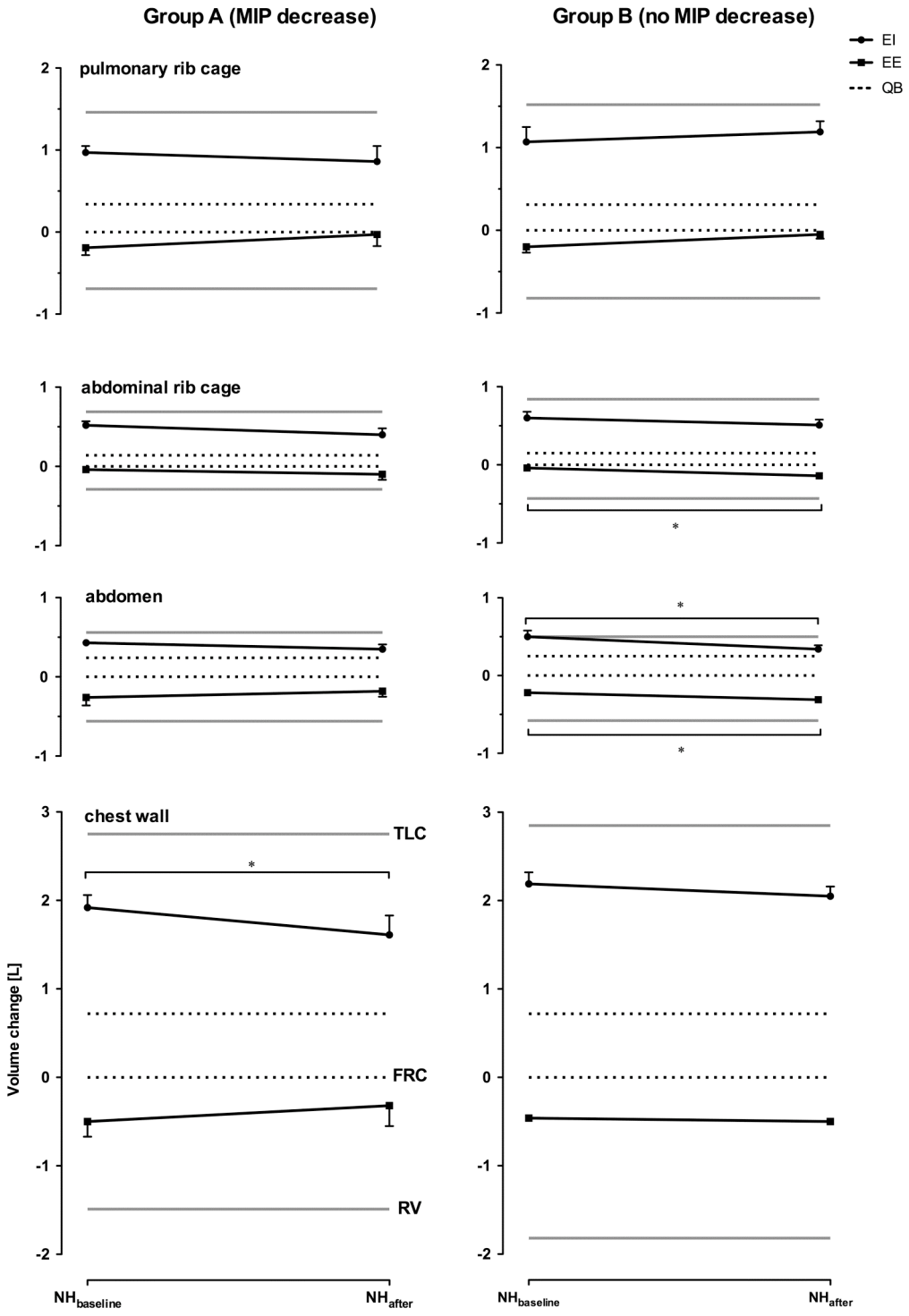


Data is given as mean ± SE. Tidal volume, breathing frequency and duty cycle for group A and B during inspiratory loaded breathing. * Significant difference within group ($p < 0.05$).

Normocapnic hyperpnea

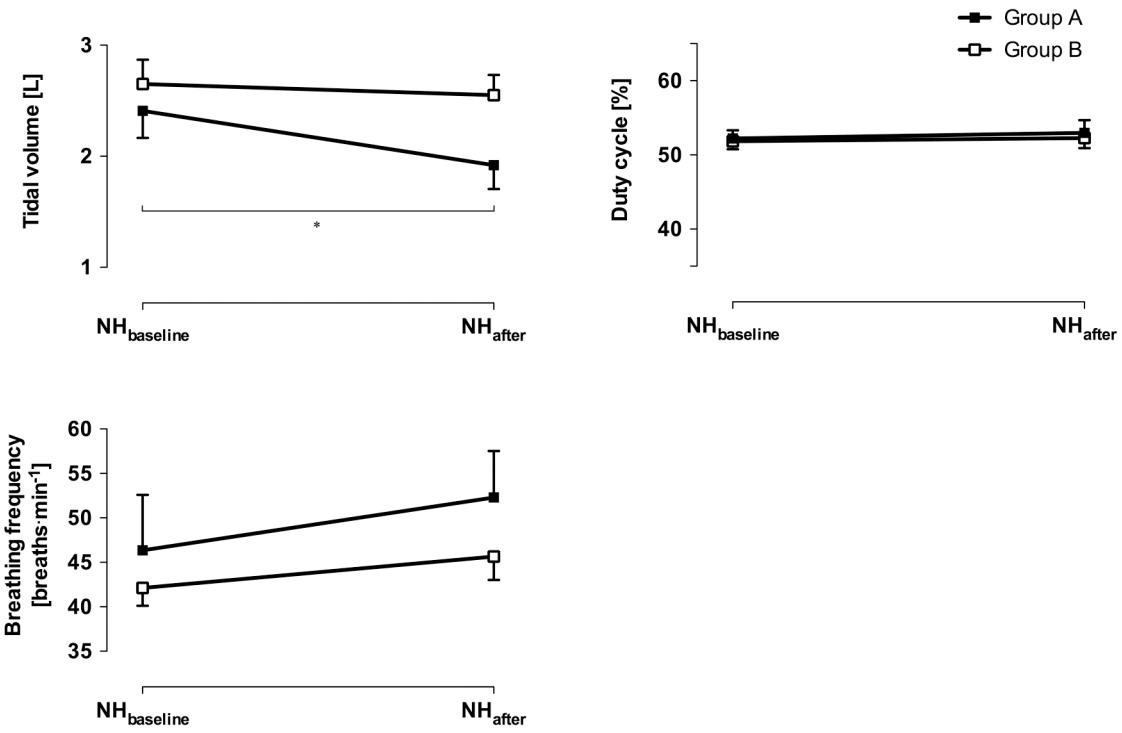
Mean end-tidal CO_2 pressure was 37 ± 3 during $NH_{baseline}$ and 37 ± 4 mmHg during NH_{after}. Mean minute ventilation during NH was not significantly different between group A ($NH_{baseline}$: 105 ± 24, NH_{after}: 96 ± 23 $L \cdot min^{-1}$, $p = 0.463$) and group B ($NH_{baseline}$: 111 ± 28, NH_{after}: 114 ± 22 $L \cdot min^{-1}$, $p = 0.600$). In group A, end-inspiratory chest wall volume was reduced during NH_{after} (Figure 7) resulting in a decreased tidal volume (Figure 8). Breathing frequency and duty cycle remained unchanged in both groups.

Figure 7. Chest wall volume changes during normocapnic hyperpnea



Data is given as mean ± SE. Changes in end-inspiratory (EI) and end-expiratory (EE) volumes, expressed relative to functional residual capacity (FRC) during normocapnic hyperpnea before ($NH_{baseline}$) and after (NH_{after}) inspiratory resistive breathing. Grey lines show maximal EI/EE volumes of the vital capacity. QB, quiet breathing; RV, residual volume; TLC, total lung capacity. * Significant difference within group ($p < 0.05$).

Figure 8. Breathing pattern during normocapnic hyperpnea



Data is given as mean ± SE. Tidal volume, breathing frequency and duty cycle for group A and B during normocapnic hyperpnea. * Significant difference within group ($p < 0.05$).

Discussion

In half of the subjects, ILB resulted in a significant decrease in MIP without a change in SNIP, reflecting a decrease in RCM strength (when assessed from RV), while in the other half, SNIP decreased significantly, without a change in MIP, reflecting most likely a decrease in diaphragmatic strength. Those subjects with a MIP-decrease after ILB lowered the EEV of the pulmonary rib cage significantly below FRC during ILB. These results indicate that predominant RCM-fatigue critically depends on the lung volume from which inspiratory efforts are initiated during ILB.

Threshold versus resistive loading

Although two different loading devices were used, inspiratory pressures, chest wall volumes and breathing pattern during ILB did not differ between subjects performing ILB with the threshold or resistive breathing device. Subjects performing ILB with the resistive device could have reduced the inspiratory effort by reducing inspiratory flow, this was not observed and there is no evidence, that changes in MIP or SNIP in response to ILB were influenced by the type of load used in the present study. However, it is to note that – despite performing ILB at comparable pressures and breathing pattern – respiratory mechanics during inspiratory efforts depend to some extent on the type of load used, i.e. during threshold loading, inspiratory flow starts only after an isovolume respiratory muscle contraction when the threshold pressure is reached while during resistive breathing, inspiratory flow is present from the start of the inspiratory phase. Although load compensation is slightly different, the present results indicate that the type of load used does not affect the change in respiratory muscle strength after ILB.

Chest wall volumes during ILB and the effects on muscle strength

By using OEP we could show for the first time the range of chest wall volume displacement during ILB over an extended period of time. Interestingly, none of the subjects breathed from RV to TLC, despite being instructed to do so. The relative contributions of the different compartments to tidal volumes did not change during ILB, but we found that differences in the EEV of the pulmonary rib cage during ILB resulted either in an MIP-decrease or an SNIP-decrease. The results suggest that lowering EEV of the rib cage below resting values by increasing expiratory rib cage (i.e. internal intercostals) muscle recruitment[32] might be responsible for the development of RCM-fatigue. Contractions of the internal intercostal muscles during expiration elongate pre-inspiratory length of the external intercostal muscles,

i.e. part of the RCM,[27] possibly instigating a range of motion which makes them more susceptible to fatigue. Support for this assumption is provided by studies showing increased sensitivity of extended muscles to fatigue.[41,96] In addition, it has been shown that exercising subjects avoid lowering EEV of the pulmonary rib cage,[4] possibly to prevent the development of RCM-fatigue.

Subjects in group B might have decreased EIV from the start to the middle to faciliate pressure generation and possibly reduce development of fatigue. This would make sense, as it is known that pressure generation capacity and endurance decrease with increasing lung volume.[12,113] The decrease of EIV of the chest wall was the consequence of lowering EIV of the pulmonary rib cage. By decreasing EIV of the pulmonary rib cage, opposing forces to the diaphragm might have been reduced, which would be an additional indicator that subjects in group B used predominantly the diaphragm. Support for this is given by the significant SNIP-decrease after ILB and the lowered EEV of the abdomen during NH since lowering EEV brings the diaphragm in a better position to generate flow.[53]

Similar to our findings, Verges *et al.*[15] observed that either predominant RCM- or diaphragm-fatigue can occur as a consequence of ILB in subjects who freely chose their breathing pattern. In their study, only subjects with predominant RCM-fatigue showed a decrease in tidal volume during subsequent exercise, as a consequence of decreased end-inspiratory lung volume, similar to subjects of group A, who lowered tidal volume during NH after ILB.

ILB and NH differ fundamentally in their contraction pattern: ILB involves high-pressure, low-speed contractions, while NH is characterized by low-pressure, high-speed contractions. During unloaded breathing at high breathing frequencies (ventilation during high-intensity

exercise or NH), total elastic work (to overcome recoil forces of the thorax) is higher compared to ILB. In this context, our results suggest that RCM seem decisive to maintain tidal volume and end-inspiratory volume high during unloaded breathing while diaphragmatic fatigue induced by ILB did not seem to affect NH performance. In fact, Romer *et al*.[99] demonstrated that after ILB-training (from RV to TLC), subjects could maintain their tidal volume and end-inspiratory volume for a longer duration during exercise compared to controls.

Breathing pattern during ILB

During ILB, the work of breathing is a function of pressure generation over time and volume. Therefore differences in breathing pattern between groups might have resulted in differences in work of breathing and consequently, changes in MIP or SNIP. However, neither breathing pattern nor pressure generation was different between groups A and B. This is in accordance with previous findings showing that during ILB, respiratory muscle fatigue does not necessarily result in an altered breathing pattern.[79] Therefore, the difference in development of respiratory muscle fatigue between groups A and B is unlikely to result from differences in work of breathing.

Limitations of the study

First, we assessed respiratory muscle fatigue by voluntary respiratory maneuvers rather than using phrenic nerve stimulation to assess changes in twitch trans-diaphragmatic pressure by use of esophageal and gastric catheters. This is because we aimed to have conditions similar to home-based training and to assure undisturbed muscle recruitment during ILB. While we are aware that voluntary maneuvers may include central fatigue, we believe that the observed MIP-decrease in group A mainly reflects peripheral RCM-fatigue, as it seems unlikely that

only subjects of group A would have exhibited central fatigue. In addition, tidal volume during NH after ILB was only reduced in group A, which we consider as an independent index of RCM-fatigue.[119]

Second, the sample size is rather small. However, as the main outcome variable was the change in MIP, which has good reproducibility, a two-sided power for detecting a 5% change of MIP was calculated to be 88% at an alpha level of 0.05 for the sample size used in our study. Therefore, we believe that our findings are not compromised by the sample size.

Third, the use of two different devices can be seen as a major concern, in particular since the use of the different devices by group A and B did not come out to be balanced. However, since changes in respiratory muscle strength after ILB were not different between the threshold and the resistive group, we believe that the development of fatigue during ILB is independent of the training device used.

Conclusions

In summary, the different effects of ILB on the development of respiratory muscle fatigue found in the present study suggest that lowering EEV of the rib cage below FRC results in predominant RCM-fatigue. As RCM are most important for inspiratory force generation, breaths should be initiated from RV during ILB. The difficulty of our subjects to follow these instructions should be considered when having healthy subjects or patients perform unsupervised ILB. Thus, providing visual feedback of lung volume during ILB should be emphasized to prevent subjects from adopting breathing strategies that minimize RCM-fatigue.

5. Reliability of non-invasive cardiac output measurement in individuals with cervical spinal cord injury

published in Spinal Cord, 2011[1]

Introduction

Cardiovascular disease is a major cause of death, also in individuals with individuals with cervical spinal cord injury (cSCI), partly due to reduced cardiorespiratory fitness.[44,90] Physical training improves cardiorespiratory fitness and associated risk factors.[9] To determine the most efficient cardiovascular training mode, to verify training effects, and to evaluate cardiovascular limitations it is important to assess cardiac function.

Although in able-bodied individuals (AB), heart rate is often used as an estimator of cardiac function during exercise, this variable is not sufficient as the only measurement in cSCI. Owing to the disturbed sympathetic nervous system, cardiovascular adaptations to exercise differ from those in AB,[74] e.g. heart rate reserve is reduced, vasomotor regulation is impaired. Thus, the measurement of cardiac output allows to better characterize cardiac function and the efficiency of cardiovascular training modalities. The primary stimulus to elicit cardiovascular training adaptations is adequate volume loading of the heart. Volume loading is, in part, reflected by the stroke volume, which can be derived from concomitant assessment of cardiac output and heart rate.

Gold standard methods such as direct Fick, dye-dilution or thermodilution to assess cardiac output are invasive, and therefore not appropriate for regular monitoring.[125] Alternatively, non-invasive techniques such as CO_2 or inert gas rebreathing can be used to measure cardiac function. Innocor^{TM} (Innovision, Odense, Denmark), a system using inert gas rebreathing,

[1] Title in Spinal Cord: Reliability of non-invasive cardiac output measurement in individuals with tetraplegia

proved to be a reliable non-invasive tool to measure cardiac output at rest[42,66,93] and during exercise in AB[42] and showed consistency with gold standard methods.[3,43,94] In addition, the Innocor™ device can estimate pulmonary shunts and evaluate the degree of gas mixing. Therefore, cardiac output might be more precisely assessed by this method than by CO_2-rebreathing.[66]

Despite being a simple and comfortable measurement procedure, a critical requirement to obtain valid measurements has been reported as being the ability to rebreathe 40% of the predicted vital capacity during four consecutive breaths within 20 s to assure complete alveolar mixing of the test gases.[69] Since tetraplegia is associated with a number of pulmonary-related impairments including compromised lung function resulting partly from the low active respiratory muscle mass,[15] feasibility of cardiac output measurement with Innocor™ needs to be evaluated in cSCI.

Although feasibility and reliability of cardiac output measurements have been previously determined during submaximal arm exercise in individuals with spinal cord injury by CO_2-rebreathing, and acceptable reliability was obtained,[89] specific analyses for cSCI were not reported and between-day reliability was not assessed. Evaluating between-day reliability is important when considering repeated cardiac output measurements in the course of a progressing disease or training. Between-day reliability may be affected by differences in sleep duration/quality, diet composition, or by the disturbed vasomotor regulation in cSCI.[74] Thus, evaluating a homogeneous group of cSCI is essential, since potential sources of measurement error might specifically relate to cSCI.

Therefore, the aim of the present study was to determine the reliability of cardiac output measurement by Innocor^{TM} at rest and during exercise in cSCI and to compare these results with AB. To test this, cSCI and AB performed cardiac output measurements on different days at rest, during arm-crank (ACE), and wheelchair exercise (WCE). We hypothesized that the reliability of cardiac output measurements at rest and during exercise would be lower in cSCI compared to AB, due to changes in autonomic function and its consequences on vasomotor regulation and cardiac control.

Materials and Methods

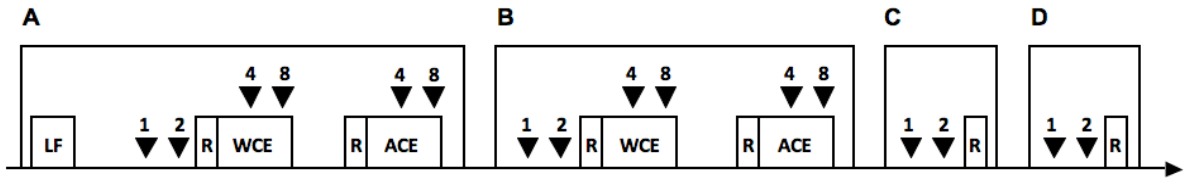
Subjects

Nine male cSCI (age 43 ± 12 yrs, height 178 ± 7 cm, body mass 69 ± 12 kg) with traumatic spinal cord injury American Spinal Injury Association Impairment Scale A or B (two C_5; three C_6; four C_7; time since injury 18 ± 11 yrs) and nine pair-matched AB (age 42 ± 12 yrs, height 177 ± 7 cm, body mass 73 ± 10 kg; all $p > 0.05$ vs. cSCI) participated in the study. Vital capacity was significantly lower in cSCI [4.1 ± 0.4 L, 85 ± 11% predicted] compared to AB [5.7 ± 1.4 L, 120 ± 30% predicted]. After detailed information about the study protocol and testing procedures, subjects gave their written informed consent. The protocol was approved by the ethics committee of the canton of Lucerne (Switzerland). The study was performed according to the Declaration of Helsinki. Subjects were required to refrain from strenuous physical activity for 48 h before the day of testing. Drinking caffeinated or alcoholic beverages on test days was forbidden and no food intake was allowed within the last 2 h before testing.

Study protocol

The experiments were conducted in four test sessions as depicted in Figure 1.

Figure 1. Experimental set-up



A - D, test sessions; LF, lung function; R, resting measurements, WCE, wheelchair exercise; ACE, arm-crank exercise; black triangles, cardiac output measurements; 1 and 2, first and second measurement at rest; 4 and 8, measurements ending at 4 min and 8 min of exercise.

Session A

Lung function was assessed according to standard procedures[124] using a body plethysmograph (MasterLab, Jaeger, Wuerzburg, Germany). After that, the pressure of the wheelchair tires was adjusted to 6.5 bar. Then, a facemask (Hans Rudolph, Shawnee, USA) and a forehead pulse oximeter sensor (8000R, Nonin Medical, Plymouth, USA) were fitted to the subjects and connected to the Innocor^{TM} system. Thereafter, three practice cardiac output measurement maneuvers without test gas were followed by two resting cardiac output measurements (A1, A2: each preceded by 5 min of quiet breathing). Afterwards, subjects were randomized and assigned to start with the ACE followed by the WCE test or *viceversa*. Both tests included 5 min of resting measurements followed by 8 min of exercise at constant loads of 15 W. The cardiac output measurements (for details, see below) were started after 3:40 min (A4) and 7:40 min (A8) of exercise. Ventilation and gas exchange were recorded breath-by-breath using the Innocor^{TM} device. The tests were separated by 20 min.

ACE tests were conducted with an electromagnetically braked, synchronous arm-crank ergometer (Ergoline, Hoechberg, Germany). The centre of the crank shaft was set at the same height as the shoulder joint of the subjects. The elbow was slightly bent when the arm was outstretched, and the hands were fixed with bandages. The workload was 15.0 ± 0.0 W and the push-rate was 61 ± 2 rpm.

WCE were conducted on a treadmill (Treadmill Giant, Bonte Technology, Groningen, Netherlands) with a moving rail to prevent potential falls from the treadmill. Before each WCE test, a dragtest was performed to determine treadmill velocity for the following WCE test. A detailed description of the drag-test can be found elsewhere.[24,115] The workload during the test was 15.2 ± 0.3 W and the push-rate was 50 ± 6 rpm. Mean velocities were 2.7 ± 0.3 and 3.0 ± 0.5 $km \cdot h^{-1}$ for cSCI and AB, respectively. The slope was set at 1.5% with two exceptions (one cSCI: 1%, one cSCI: 2%).

Session B

Session B was identical to Session A.

Sessions C and D

Resting measurements were performed similar to sessions A and B. Thereafter, exercise tests were performed that do not belong to the scope of the present study. However, resting values of these two sessions were included to investigate potential systematic errors due to learning effects over repeated sessions.

Cardiac output measurement using Innocor™

Prior to the cardiac output measurement, a rebreathing bag was filled with a specific gas mixture consisting of 28% oxygen, 0.5% nitrous-oxide and 0.1% sulphur-hexafluoride in nitrogen from athmosperic air. The filling volume was set at 40% of the subjects' predicted vital capacity. If this was not achieved by the cSCI, then the filling volume was set at 44% of the effective vital capacity for cSCI. cardiac output measurements were performed at a breathing frequency of 18 - 22 breaths per minute over a maximum of 20 s. Heart rate was derived from the pulse oximeter. Stroke volume was derived from cardiac output and heart rate. Cardiac output measurements were carried out by one operator.

Data analysis

Within- and between-day reliability were evaluated by calculating the bias (difference between two measurements) ± 95% limits of agreement (LOA: ± 1.96 x standard deviation (s.d.) of the bias), coefficients of variation (CVs), and intra-/interclass correlation coefficients (ICCs) as suggested by Atkinson and Nevill.[6]

First, we performed repeated measures ANOVA with Bonferroni-Holm correction for between- and within-pairs bias for resting values and paired t-tests for exercise data. As no significant differences were found and bias ± LOA for the separate sessions were similar, within-day pairs for resting values (A1/A2, B1/B2, C1/C2, D1/D2) were pooled.[61] Similarly, within-day pairs of exercise values (A4/A8, B4/B8) were pooled. The same was carried out for between-day pairs of resting (A1/B1, A2/B2, C1/D1, C2/D2) and exercise values (A4/B4, A8/B8). We then recalculated the bias ± LOA for the pooled data. CVs (100 x (s.d.)/mean) were calculated for each session separately and then averaged. ICCs were calculated using a one-way random effects model, expressed as single measures reliability.

Absolute physiological values were evaluated by using paired and unpaired t-tests to test for significant differences within, or between, different conditions, and between cSCI and AB. For this purpose, oxygen consumption was averaged over the second to fourth minute at rest, and over 30 s before the start of the cardiac output measurement during exercise. Then oxygen consumption and hemodynamic parameters of resting measurements in sessions A - D were averaged, and exercise values for sessions A and B were averaged for arm-crank and WCE separately.

Analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, USA) and Prism 5.0 (GraphPad, San Diego, USA) and statistical significance was accepted for $p < 0.05$.

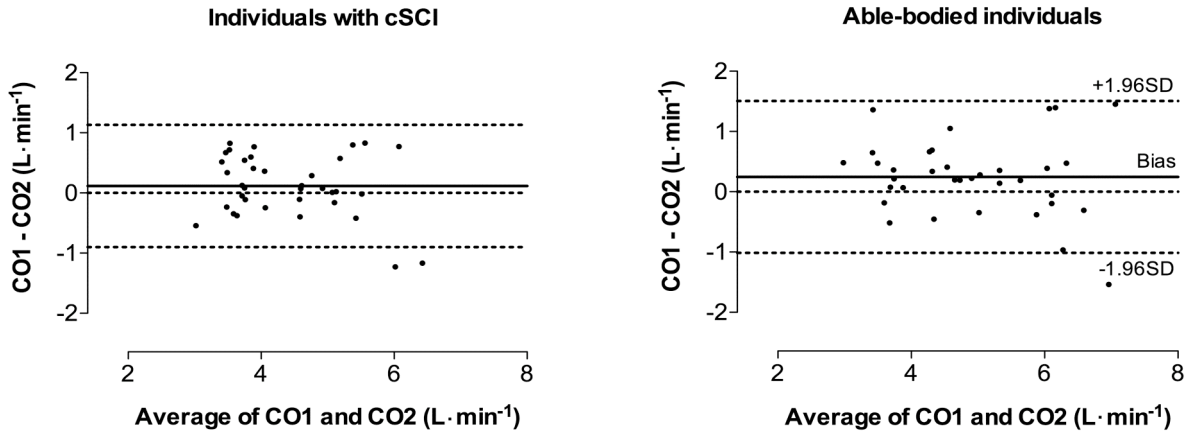
Results

From a total of 144 cardiac output measurements in each group, nine cardiac output measurements had to be excluded (cSCI: n = 4; AB: n = 5) due to incomplete gas mixing or technical problems.

Bias ± 95% limits of agreement

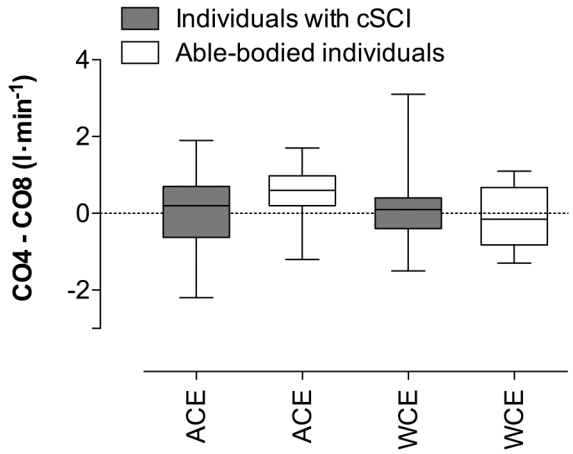
Within-day cardiac output bias at rest (Figure 2) and during exercise (Figure 3) were not significantly different between cSCI and AB (all $p > 0.05$). Between-day LOAs were wider compared to within-day LOAs for all measures and conditions (Table 1).

Figure 2. Bland-Altman plot of within-day cardiac output comparisons at rest



Results of duplicate cardiac output measurements at rest (measurements: n = 72 in individuals cSCI, n = 70 in able-bodied individuals). The differences of two measurements are plotted against their mean value. cSCI, cervical spinal cord injury; CO, cardiac output.

Figure 3. Bias of within-day cardiac output comparisons during exercise



Mean difference (bias) between cardiac output measurements ending at 4 min and 8 min of exercise (measurements: arm-crank exercise, n = 34; wheelchair exercise, n = 30 in individuals with cSCI; arm-crank exercise, n = 34; wheelchair exercise n = 30 in able-bodied individuals). cSCI, cervical spinal cord injury; CO, cardiac output; ACE, arm-crank exercise; WCE, wheelchair-exercise.

Coefficients of variation

CVs are shown in Table 2. Within-day cardiac output CVs in cSCI were generally smaller in resting compared to exercise measurements (rest 6.8, ACE 9.6, WCE 10.8%). The highest CVs were found for stroke volume during exercise in cSCI. The smallest CVs were found for heart rate in both groups for all conditions.

Intra- and interclass correlation coefficients

ICCs are shown in Table 3. Overall ICCs were slightly lower in cSCI compared to AB.

Hemodynamic parameters and oxygen consumption

Cardiac output, heart rate, and oxygen consumption were significantly greater during exercise compared to at rest in both groups (Table 4), and were greater for AB compared to cSCI. Stroke volume increased during exercise in AB but not in cSCI.

Table 1. Bias and 95% limits of agreement at rest, during arm-crank and wheelchair exercise

	Individuals with cSCI			Able-bodied individuals		
	Rest	**Arm-crank**	**Wheelchair**	**Rest**	**Arm-crank**	**Wheelchair**
Within-day						
CO, $L \cdot min^{-1}$	0.1 [-0.9-1.1]	0.1 [-1.7-1.9]	0.3 [-2.2-2.7]	0.2 [-1.0-1.5]	0.5 [-0.9-1.9]	-0.1 [-1.7-1.4]
SV, mL	1.6 [-15.7-18.9]	-1.3 [-27.0-24.4]	6.3 [-41.7-54.2]	4.0 [-14.7-22.7]	6.3 [-9.3-21.9]	1.3 [-19.2-21.7]
HR, min^{-1}	0.8 [-6.2-7.9]	3.0 [-4.5-10.5]	-3.0 [-17.7-11.7]	-0.4 [-6.3-5.5]	0.0 [-4.5-4.5]	-2.4 [-8.0-3.2]
Between-day						
CO, $L \cdot min^{-1}$	-0.7 [-1.9-0.6]	-0.3 [-2.5-1.9]	0.1 [-2.1-2.3]	-0.1 [-1.8-1.6]	0.0 [-2.3-2.3]	0.5 [-1.4-2.4]
SV, mL	-7.4 [-27.1-12.1]	-1.2 [-36.3-33.9]	6.9 [-45.9-59.8]	-0.6 [-30.9-29.8]	-2.7 [-31.7-26.4]	2.8 [-18.8-24.3]
HR, min^{-1}	-2.7 [15.5-10.1]	-1.7 [-15.1-11.7]	-7.7 [-33.2-17.7]	-0.7 [-14.1-12.7]	0.2 [-8.3-8.7]	1.9 [-13.7-17.6]

Data is given as mean bias [upper - lower 95% limits of agreement]. Bias: difference between two measurements; limits of agreement: test-retest differences for 95% of a population, the upper/lower limit of agreement correspond to "bias ± (1.96 x [standard deviation of bias])". cSCI, cervical spinal cord injury; CO, cardiac output; SV, stroke volume; HR, heart rate.

Table 2. Coefficients of variation at rest, during arm-crank and wheelchair exercise

	Individuals with cSCI			Able-bodied individuals		
	Rest	**Arm-crank**	**Wheelchair**	**Rest**	**Arm-crank**	**Wheelchair**
Within-day						
CO	6.8 [4.8-8.1]	9.6 [8.2-10.9]	10.8 [6.2-15.4]	7.7 [5.5-11.1]	6.8 [5.6-7.9]	6.0 [5.9-6.1]
SV	7.1 [5.2-8.0]	10.4 [8.7-12.0]	14.7 [7.7-21.7]	7.5 [5.5-11.2]	7.0 [6.4-7.6]	6.6 [6.3-6.7]
HR	3.0 [2.7-3.5]	3.2 [2.8-3.5]	4.7 [2.5-6.9]	2.1 [1.3-3.5]	1.8 [1.5-2.0]	2.3 [1.8-2.8]
Between-day						
CO	11.9 [9.0-13.1]	11.2 [8.5-13.8]	10.3 [8.4-12.1]	9.2 [7.0-12.1]	8.5 [7.9-8.9]	8.0 [7.1-8.9]
SV	9.8 [8.5-11.0]	14.3 [11.8-16.7]	16.2 [11.0-21.3]	10.5 [8.6-12.1]	8.1 [7.6-8.5]	7.0 [6.7-7.2]
HR	7.0 [5.6-8.1]	4.8 [4.4-5.1]	8.8 [5.8-11.7]	5.3 [4.2-6.0]	3.8 [3.7-4.0]	4.0 [3.7-4.3]

Data is given as the mean coefficient of variation in percentage [smallest and highest CV of the single sessions]. cSCI, cervical spinal cord injury; CO, cardiac output; SV, stroke volume; HR, heart rate.

Table 3. Intra- and interclass correlation coefficients

	Individuals with cSCI			Able-bodied individuals		
	Rest	**Arm-crank**	**Wheelchair**	**Rest**	**Arm-crank**	**Wheelchair**
Intraclass c. c.						
CO	0.84 [0.71-0.91]	0.75 [0.35-0.91]	0.37 [-0.84-0.78]	0.84 [0.71-0.91]	0.93 [0.80-0.97]	0.92 [0.79-0.97]
SV	0.90 [0.81-0.95]	0.76 [0.37-0.91]	0.55 [-0.30-0.85]	0.79 [0.64-0.89]	0.94 [0.83-0.98]	0.91 [0.75-0.97]
HR	0.94 [0.89-0.97]	0.94 [0.85-0.98]	0.87 [0.64-0.96]	0.94 [0.89-0.97]	0.98 [0.94-0.99]	0.96 [0.90-0.99]
Interclass c. c.						
CO	0.51 [0.25-0.71]	0.57 [-0.13-0.84]	0.60 [-0.14-0.87]	0.75 [0.56-0.87]	0.87 [0.62-0.96]	0.84 [0.54-0.94]
SV	0.80 [0.65-0.89]	0.43 [-0.50-0.78]	0.36 [-0.84-0.78]	0.54 [0.26-0.74]	0.87 [0.61-0.95]	0.89 [0.69-0.96]
HR	0.79 [0.63-0.89]	0.87 [0.66-0.95]	0.19 [-1.33-0.73]	0.70 [0.49-0.84]	0.88 [0.66-0.96]	0.90 [0.73-0.97]

Data is given as single measures value [lower - upper bound 95% confidence interval]. cSCI, cervical spinal cord injury; CO, cardiac output; SV, stroke volume; HR, heart rate.

Table 4. Hemodynamic parameters and oxygen consumption at rest and during submaximal exercise

	Individuals with cSCI			Able-bodied individuals		
	Rest	**Arm-crank**	**Wheelchair**	**Rest**	**Arm-crank**	**Wheelchair**
CO, $L \cdot min^{-1}$	4.4 ± 0.8	5.4 ± 0.8	5.4 ± 1.0	4.9 ± 1.1	7.5 ± 1.5*	8.1 ± 1.3*§
SV, mL	72 ± 18	70 ± 11	68 ± 20	70 ± 14	90 ± 20*	95 ± 16*
HR, min^{-1}	63 ± 10	78 ± 10	81 ± 9	70 ± 8	82 ± 8	84 ± 9
$\dot{V}O_2$, $L \cdot min^{-1}$	0.24 ± 0.04	0.62 ± 0.07	0.64 ± 0.06	0.29 ± 0.04*	0.73 ± 0.07*	0.84 ± 0.09*§

Data is given as mean ± SD. cSCI, cervical spinal cord injury; CO, cardiac output; SV, stroke volume; HR, heart rate; $\dot{V}O_2$, oxygen consumption. * $p < 0.05$, significant difference between individuals with cSCI and able-bodied individuals. § $p < 0.05$ significant difference between arm-crank and wheelchair exercise. All values during exercise were significantly higher compared to resting values except for the stroke volume for individuals with cSCI.

Discussion

Non-invasive cardiac output measurement assessed with Innocor™ demonstrated acceptable reliability at rest and during exercise. Our hypothesis, that the reliability of cardiac output measurements in cSCI compared to AB would be lower was rejected. Thus, differences in cardiovascular control between cSCI and AB did not substantially affect the reliability of these measurements.

Although cSCI showed lower ICCs compared to AB, ICCs should be interpreted with caution since they have the major limitation of depending heavily on the range of values and they are specific for the individuals in this sample only. The consideration of the CVs might therefore be more relevant since they cover 68% of the variability that is actually present in repeated measurements for an average individual. CVs of cardiac output at rest (cSCI: 6.8; AB: 7.7%) in our study demonstrated good reliability compared to gold standard methods where within-day CVs are generally 5 - 10%.[125]

Furthermore, CVs of resting assessments in cSCI and AB compare well with those of Fontana *et al.*[42] who found within-day CVs of 8.6% and between-day CVs of 10.0% in resting AB using the Innocor™ system. During submaximal leg exercise in AB, Fontana *et al.*[42] found CVs ranging from 4.3 to 6.4% while CVs during arm exercise in the present study appeared slightly higher (cSCI: 9.6 - 11.2; AB: 6.0 - 8.5%). Arm movements represent a possible source of error during rebreathing. In particular, cSCI rely also on arm and upper chest muscles to support respiration.[77] However, the importance of these considerations seems negligible, since CVs were still in an acceptable range compared to other invasive or non-invasive methods for cardiac output determination.[125]

We observed that the major contribution to cardiac output variability originated from stroke volume variability, shown by higher CVs in stroke volume compared to heart rate, where CVs were constantly low in both groups. In addition, cSCI had slightly higher stroke volume CVs than AB, possibly because of larger breathing irregularities with arm exercise compared to AB, leading to transient changes in intrathoracic or intraabdominal pressure swings[127], or abnormal vasomotor regulation, both factors that could influence venous return and therefore stroke volume.

Interestingly, absolute physiological responses to exercise were different between cSCI and AB, despite using the same exercise protocol. For example, stroke volume did not increase in cSCI in contrast to AB. This lack of increase with exercise likely results from a lack of increase in venous return related to an inefficient vasoconstrictor-response in non-working muscles. Apparently, the reliability of cardiac output measurements is independent of the magnitude of the values in this setting, shown by comparable measures of reliability in cSCI and AB.

Clinical relevance

We conclude that the Innocor^{TM} device is suitable for routine cardiac output assessment since familiarization and measurement procedures are not time consuming, systematic errors due to learning effects were not observed, and the quality of the obtained measurement can be easily verified by adhering to strict criteria. To evaluate cardiac function in cSCI, heart rate, as a single measure, is not sufficient due to cardiovascular restrictions related to the changed function of the autonomic nervous system. Therefore, cardiac output measurements are necessary to obtain important information (e.g. stroke volume) of the cardiovascular response to exercise and/or training to ultimately enhance cardiovascular health in cSCI.

Concerning the reliability of the cardiac output measurements, a certain amount of random error due to biological or mechanical variations cannot be avoided, thus, is the Innocor™ device precise enough to be of practical use to assess cardiac output in cSCI? From the present data, LOAs predict that 95% of future cardiac output measurements will deviate between -0.9 - 1.1 $L \cdot min^{-1}$ in cSCI and -1.0 - 1.5 $L \cdot min^{-1}$ in AB from a previous measurement. These values are similar compared to the values found by Peyton *et al.*[93] in AB (-0.88 - 0.88 $L \cdot min^{-1}$) using Innocor™. In view of the present results, we support those authors recommendation to perform two or more measurements (depending on the degree of precison needed) and to use the average of these measurements when assessing cardiac function. Importantly, Atkinson and Nevill[6] pointed out that it is the task of the scientist, physician or coach to judge whether LOAs are narrow enough for the test to be of practical use. In order to decide, it might be helpful to calculate the sample size required to detect between-day cardiac output changes of 1.5 - 2.0 times the CV[61] for future cardiac output measurements. Based on current findings, a training study able to detect cardiac output changes of 15% during exercise, calculated based on 80% power and a two-sided test with $p < 0.05$ for significance, would need to include thirteen cSCI.

Technological Considerations

First, the sample size in our study was small, but the inclusion criteria restricted the available number of active and otherwise healthy volunteers with tetraplegia. To partly overcome this issue, we increased the number of sessions to improve statistical power and we included a matched group of AB for comparison.

Second, our findings account for submaximal exercise. It might be easier to perform the rebreathing maneuvers at submaximal exercise compared to maximal exercise, where for example the coordination could be more challenging, particularly for cSCI. Also, at maximal

arm exercise, measurement errors due to arm movements, or breathing irregularities might be more pronounced.

Third, our study design does not address the validity of cardiac output measurements with Innocor™ in cSCI. As determination of the validity would require cardiac catheterization to compare cardiac output measurements of Innocor™ with cardiac output measurements from the Fick method, we reasoned that the invasiveness of the measurement would reduce the pool of available volunteers wanting to participate in our study. In addition, the risks and possible complications associated with heart catheterization and a sudden occurrence of autonomic dysreflexia would not warrant its use in healthy cSCI.

Conclusions

In summary, Innocor™ provides reliable cardiac output measurements for cSCI at rest and during exercise. These results add to the existing literature related to inert gas rebreathing by providing within- and between-day reliability analyses of cardiac output and stroke volume during exercise. Innocor™ provides a non-invasive alternative for routine evaluation of cardiac function as well as for monitoring progression of disease or improvement of cardiac function during rehabilitation or training in cSCI.

6. Maximal cardiac output during exercise after cervical spinal cord injury

submitted for publication

Introduction

Transection of the cervical spinal cord leads to altered cardiovascular regulation during exercise.[39,58,65,95] First, heart rate during exercise has been reported to be restricted to 120 - 130 min^{-1} in subjects with motor complete cervical spinal cord injury (cSCI)[10,31,60] resulting from the lack of supraspinal sympathetic nervous outflow directed to the heart.[74] Second, low concentrations of plasma catecholamines[28,104] prevent vasoconstriction in the non-exercising tissues. As a result, ineffective blood redistribution[63,111] and hypotension[71] are likely to occur during exercise in cSCI and these factors have been associated with venous blood pooling in the lower extremities.[104] This may, in turn, impair venous blood return to the heart and affect stroke volume.[39,70]

Impaired cardiovascular regulation and extensive skeletal muscle paralysis reduce exercise tolerance and compromise effective cardiovascular training. As a result, deconditioning and a sedentary lifestyle increase the risk of cardiovascular disease in cSCI.[44,90] Regular physical exercise is known to improve many cardiovascular risk factors (e.g. blood lipid profile, insulin sensitivity, visceral fat).[31,65] However, to determine the most efficient cardiovascular training mode, it is important to evaluate cardiac output and stroke volume in response to exercise.

Several studies measured cardiac output in cSCI. However, they only assessed submaximal exercise responses.[28,40,57,63,84] They reported elevated cardiac output and unchanged stroke volume in response to submaximal arm exercise training[84] or increased cardiac output and

stroke volume during leg exercise by use of functional electric stimulation.[28,40,63] However, the magnitude of cardiac output and stroke volume changes in response to maximal arm exercise in a homogeneous group of cSCI is yet unknown.

Therefore, the primary aim was to determine maximal cardiac output and stroke volume during arm-crank (ACE) and wheelchair exercise (WCE), which are common training modalities in cSCI. This information is necessary to determine the exercise mode with the highest potential to elicit training-induced central cardiovascular adaptations with – for example – high intensity interval training. We reasoned that differences in metabolic (e.g. oxygen demand) or mechanical (e.g. propulsion technique, breathing pattern) properties between ACE and WCE might affect cardiac output and stroke volume differently.

Furthermore, we aimed to determine the factors that are relevant to exercise tolerance by comparing the respiratory demand, ratings of perceived exertion (RPE), and oxygen uptake between ACE and WCE. We also compared cSCI to pair-matched able bodied subjects (AB) to determine the type of limitation specifically related to cSCI.

Materials and Methods

Subjects

Nine men with traumatic spinal cord injury American Spinal Injury Association Impairment Scale A or B (two C_5; three C_6; four C_7; time since injury 18 ± 11 yrs) and nine pair-matched AB participated in the study. Subjects were matched for age, body mass, and physical activity. Subject characteristics are shown in Table 1. After detailed information about the study protocol and testing procedures, subjects gave their written informed consent. The protocol was approved by the ethics committee of the canton of Lucerne (Switzerland). The study was performed according to the Declaration of Helsinki. Subjects were required to

refrain from strenuous physical activity for 48 h before the day of testing. Drinking caffeinated or alcoholic beverages on test days was forbidden and no food intake was allowed within the last 2 h before testing.

Table 1. Subject characteristics

	Individuals with cSCI	**Able-bodied individuals**	p - value
Age, yrs	43 ± 12	42 ± 12	0.825
Height, cm	178 ± 7	177 ± 7	0.824
Body mass, kg	69 ± 12	73 ± 10	0.400
Activity, $h \cdot week^{-1}$	6.5 ± 3.0	4.6 ± 0.9	0.190
VC, %predicted	85 ± 11	120 ± 30	0.001
TLC, %predicted	90 ± 13	107 ± 23	0.019
RV, %predicted	116 ± 38	95 ± 36	0.085
FEV_1, %predicted	83 ± 12	109 ± 25	0.002
PEF, %predicted	77 ± 18	110 ± 28	0.003

Values are mean ± SD. cSCI, cervical spinal cord injury; VC, vital capacity; TLC, total lung capacity; RV, residual volume, FEV_1, forced expiratory volume in 1s; PEF, peak expiratory flow.

Study protocol

All subjects reported to the laboratory on three separate days. During the initial visit, subjects were familiarized with test procedures and instrumentation. Then, lung function was assessed according to standard procedures[124] using a body plethysmograph (MasterLab, Jaeger, Würzburg, Germany). During the second and third visit, all subjects performed graded ACE or WCE to exhaustion (for details see below). The order of the test modes was randomized and balanced.

General exercise testing procedures

Upon arrival at the laboratory, subjects were asked to empty their bladder, then body weight was measured, and tire pressure of the wheelchair was adjusted to 6 bar. After that, subjects were fitted with a forehead oxygen saturation sensor (8000R, Nonin Medical, Plymouth, USA) and with a facemask (Hans Rudolph, Shawnee, USA) which was connected to the Innocor^{TM} system (Innovision, Odense, Denmark). The Innocor^{TM} system was used to measure ventilation and gas exchange breath-by-breath, and to determine cardiac output at rest and during exercise. All test protocols included at least three practice measurements of cardiac output, and two cardiac output measurements at rest, each preceded by 5 min of quiet breathing. During exercise, cardiac output was assessed at maximal exercise (for details see below) and RPE was assessed every minute using a 10 - point scale.[11] Numbers were read aloud and the subject nodded when the appropriate number was named. Blood pressure was measured at rest and immediately after exercise using an automated arm cuff (Omron, HEM-907, Omron Healthcare, England). Capillary blood samples (20 μl) were collected from the earlobe before the start of the exercise test, as well as 2 min and 4 min after exercise for the assessment of blood lactate concentration (Super GL, Ruhrtal Labor Technik, Möhnesee, Germany).

Maximal exercise test protocol

Maximal ACE and WCE protocols started at 3 W with increments of 3 ± 0 W·min^{-1} for ACE and 3 ± 1 W·min^{-1} for WCE until subjects reached volitional exhaustion. Initial treadmill speed was set at 1 km·h^{-1} at an inclination of 1%. Treadmill speed was increased by 0.5 km·h^{-1} for the two subsequent increments followed by an increase in inclination of 0.5%. Alternate changes in speed and inclination were continued until volitional exhaustion. The measurement of maximal cardiac output was initiated 30 s before subjects reached

exhaustion. Since we expected AB to attain higher maximal work loads, incremental tests in cSCI were scheduled before those of AB, so that an additional cardiac output measurement could be performed in AB at the workload identical to the maximal workload achieved by the matched cSCI (isomax).

ACE and WCE equipment and settings

ACE tests were conducted with an electromagnetically braked, synchronous arm-crank ergometer (Ergoline, Höchberg, Germany). The center of the crank shaft was set at the height of the subject's shoulder joint. The elbow remained slightly bent when the arm was outstretched. Elastic straps were used to fix the hands to the handles of the ergometer.

WCE tests were conducted on a motor-driven treadmill (Treadmill Giant, Bonte Technology, Groningen, Netherlands) with a moving rail to prevent potential falls from the treadmill. A separate dragtest was performed before WCE started. Details of the dragtest can be found elsewhere.[24,115] cSCI performed all tests in their own wheelchair. Chest straps or gloves were used if needed. AB performed all tests in the same standard wheelchair and were instructed to use mainly the heel of the hand for propulsion, similar to cSCI, and to relax chest wall and leg muscles.

Cardiac output assessment

The technology of the Innocor^{TM} system to assess cardiac output is based on inert gas rebreathing using nitrous-oxide and sulphur-hexafluoride. The theoretical basis for this non-invasive technique, its application, and validity for exercise testing have been previously described.[3,18,42] Briefly, prior to the cardiac output measurement, a rebreathing bag was filled with a specific gas mixture consisting of 28% oxygen, 0.5% nitrous-oxide and 0.1% sulphur-

hexafluoride in nitrogen from atmospheric air. The filling volume was set at 40% of the subjects' predicted vital capacity. If this was not achieved by the cSCI, then the filling volume was set at 44% of the effective vital capacity for cSCI. Cardiac output measurements were performed at a breathing frequency of 18 - 22 breaths per minute over a maximum of 20 s. Heart rate was measured by pulse oximetry and stroke volume was derived from cardiac output and heart rate.

Data analysis

Resting cardiac output measurements were averaged. Breath-by-breath data of physiological variables were averaged over 30 s intervals. The maximal workload was determined as the highest workload that was sustained for at least 30 s. The Wilcoxon sign rank test was used for pairwise comparisons of hemodynamic data assessed at rest and during exercise. Between-group comparisons were performed using the Mann-Whitney U test. Analyses were perfomed using SPSS 17.0 (SPSS Inc., Chicago, USA) and statistical significance was accepted for $p < 0.05$. Data is given as mean ± standard deviation (SD) if not otherwise stated.

Results

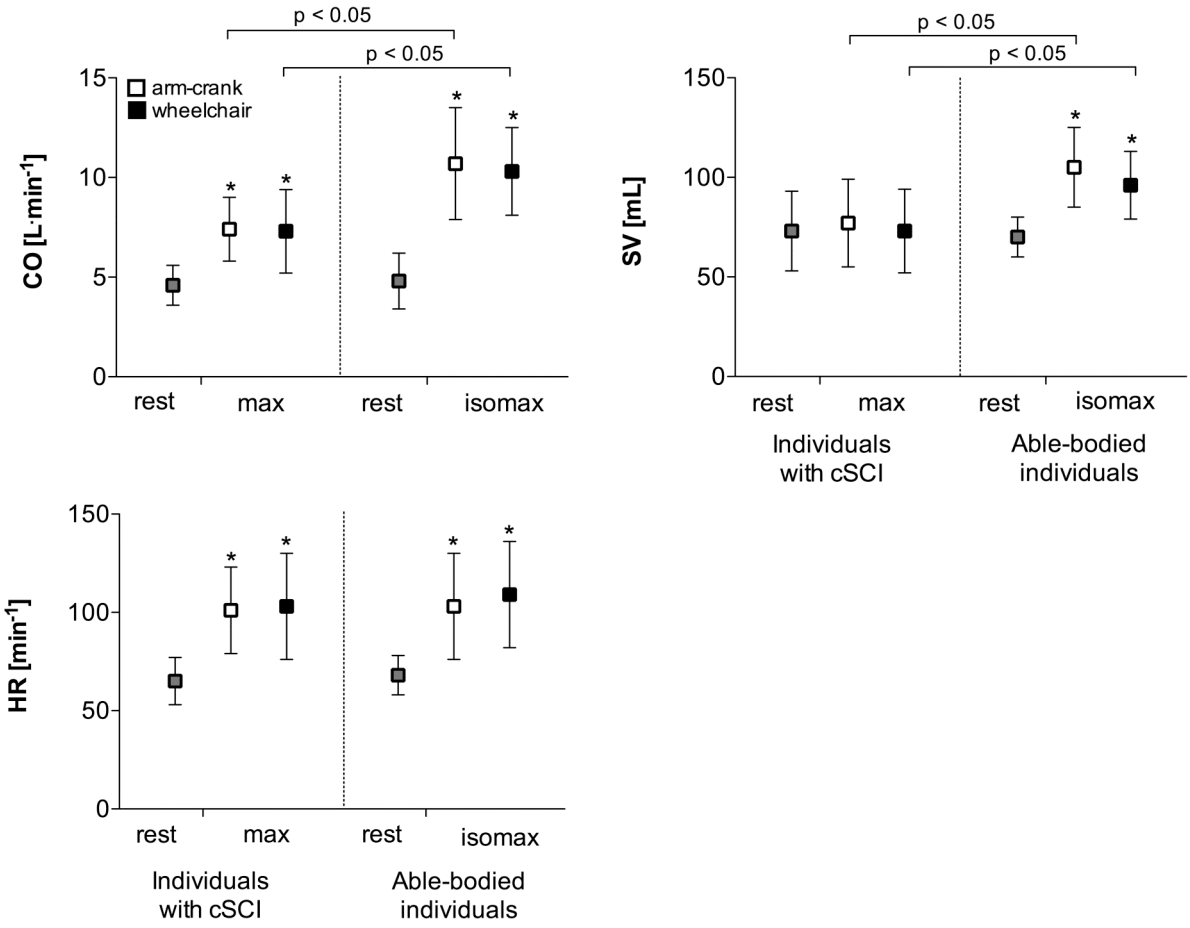
In AB, three maximal cardiac output measurements had to be excluded due to technical problems. Therefore, comparisons of maximal hemodynamics are reported for $n = 6$ in AB.

Maximal hemodynamics in cSCI compared to AB at identical workloads

Figure 1 shows that maximal hemodynamic responses to exercise were not different between ACE and WCE in cSCI. While at maximal exercise, cardiac output and heart rate were significantly increased compared to rest, stroke volume and blood pressure (Table 2) did not

differ from resting values (blood pressure: systolic 103 ± 15, diastolic 60 ± 11 mm Hg). Maximal heart rate of cSCI did not differ from heart rate at identical workloads in AB, while cardiac output and stroke volume were significantly lower in cSCI compared to AB.

Figure 1. Hemodynamic responses to arm exercise



Values are mean ± SD. SCI, spinal cord injured; max, maximal workload in SCI; isomax, workload in able-bodied identical to max; CO, cardiac output; SV, stroke volume; HR, heart rate. * $p < 0.05$ significant difference between rest and exercise.

Exercise responses in cSCI compared to AB at identical workloads

Table 2 shows maximal ACE and WCE data of cSCI in. Eight out of nine cSCI achieved higher workloads during ACE compared to WCE. Otherwise, no differences were found in maximal responses between ACE and WCE.

End-tidal carbon dioxide pressure during maximal exercise was significantly lower compared to rest (rest 38 ± 3, exercise 32 ± 5 mm Hg) and compared to AB at isomax (rest 37 ± 2, exercise 38 ± 2 mm Hg). The ventilatory equivalent for oxygen was significantly higher at maximal exercise for cSCI compared to AB at isomax (cSCI 50 ± 9, AB 33 ± 4).

Table 2. Maximal values during incremental exercise tests in individuals with cervical spinal cord injury

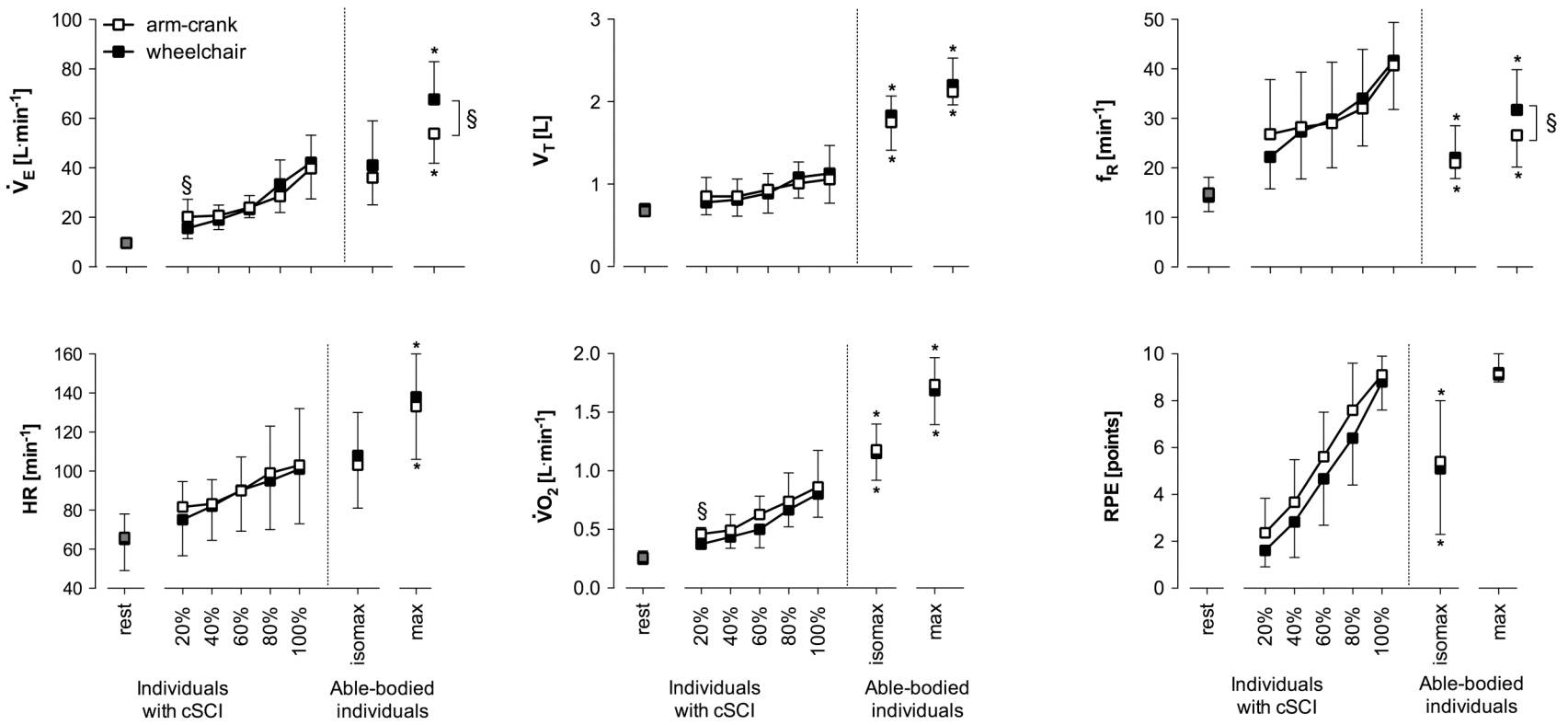
	Individuals with cSCI		
	Arm-crank	**Wheelchair**	p - value
Workload, W	42 ± 17	31 ± 13	0.015
Push rate, rpm	60 ± 3	65 ± 13	0.441
$\dot{V}O_2$, $mL \cdot kg^{-1} \cdot min^{-1}$	15 ± 7	14 ± 5	0.383
SpO_2, %	98 ± 1	98 ± 2	0.489
L_a, $mmol \cdot L^{-1}$	3.1 ± 1.8	3.3 ± 1.8	0.767
BP systolic, mm Hg	96 ± 18	95 ± 38	0.953
BP diastolic, mm Hg	54 ± 19	47 ± 15	0.176

Values are mean ± s.d. Peak responses to incremental arm-crank and wheelchair exercise in individuals with cervical spinal cord injury. cSCI, cervical spinal cord injury (n = 9); $\dot{V}O_2$, oxygen uptake; SpO_2, arterial oxygen saturation; L_a, blood lactate concentration; BP, blood pressure.

Figure 2 shows that all exercise responses were elevated compared to rest and continued to increase with exercise intensity. For cSCI, the increase in tidal volume from rest to maximal exercise was only 0.4 ± 0.1 L and absolute tidal volume did not exceed 1.1 ± 0.4 L (in

percent of vital capacity: ACE 26 ± 9, WCE 28 ± 8%). Accordingly, increases in minute ventilation were predominantly achieved through increases in breathing frequency. Conversely, oxygen uptake and tidal volume were higher in AB and breathing frequency was lower compared to cSCI at the same minute ventilation.

Figure 2. Physiological responses and ratings of perceived exertion during graded arm exercise



Values are mean ± SD. cSCI, cervical spinal cord injury; max, maximal workload; isomax, maximal workload of the cervical SCI; 20 - 80%, workload in % of the maximal workload (100%); $\dot{V}_E$, minute ventilation; V_T, tidal volume; f_R, breathing frequency, HR, heart rate; $\dot{V}O_2$, oxygen uptake; RPE, ratings of perceived exertion. § $p < 0.05$ significant difference between arm-crank and wheelchair exercise.* $p < 0.05$ significantly different from 100% of cSCI.

Maximal exercise responses in AB

Table 3 shows hemodynamic responses to maximal ACE and WCE for the six AB. Maximal workload (n = 9) for ACE (73 ± 14 W) was significantly higher compared to WCE (53 ± 11 W). Maximal heart rate, oxygen uptake, blood lactate concentration (ACE 4.4 ± 1.7, WCE 5.1 ± 1.4 mmMol·L^{-1}), and tidal volume relative to vital capacity (ACE 38 ± 9, WCE 39 ± 6%) were similar for ACE and WCE and were significantly higher compared to cSCI. Maximal minute ventilation and breathing frequency were lower for ACE compared to WCE. Maximal minute ventilation was higher while breathing frequency was lower in AB compared to cSCI (Figure 2).

Table 3. Maximal hemodynamic responses to incremental exercise in able-bodied individuals

	Able-bodied individuals		
	Arm-crank	**Wheelchair**	p - value
CO, L·min^{-1}	12.1 ± 2.4	13.1 ± 2.3	0.345
SV, mL	83 ± 14	91 ± 21	0.345
HR, min^{-1}	146 ± 24	144 ± 16	0.344
BP systolic, mm Hg	160 ± 30	165 ± 33	0.465
BP diastolic, mm Hg	72 ± 8	78 ± 9	0.223

Values are mean ± SD. Hemodynamic responses to maximal arm-crank and wheelchair exercise in able-bodied individuals (n = 6). CO, cardiac output; SV stroke volume; HR, heart rate; BP; blood pressure.

Discussion

There are two main findings in this study. First, we demonstrate that during graded exercise to exhaustion, maximal hemodynamic and respiratory responses did not differ between ACE and WCE in cSCI. Second, the increase in cardiac output was achieved by an increase in heart rate, while stroke volume remained near pre-exercise levels at maximal exercise in cSCI.

These findings have both physiological and practical relevance. From the physiological point of view, it appears that the limits to increase cardiac output are governed by the restrictions to increase heart rate and stroke volume, which are most likely a consequence of the disturbed sympathetic nervous system in cSCI. The fact that stroke volume increased at isomax in AB confirms that this intensity of upper body exercise has, in general, the potential to increase stroke volume. In practice, these findings support the view that conventional ACE and WCE exercise might not provide an adequate training stimulus to elicit central training adaptations in cSCI.[39,95]

Exercise tolerance in cSCI

Peak oxygen uptake in cSCI was within the average range for this population.[67] In addition, a substantial contribution of anaerobic energy supply to maximal exercise performance was present, shown by increased blood lactate concentration, increased ventilatory equivalent for oxygen, and low end-tidal carbon dioxide pressure at maximal exercise.

Low active muscle mass and high muscle fatigability are commonly presumed to be the major limiting factor for exercise performance in cSCI.[39,62,95,103,110] However, since stroke volume and blood pressure did not increase above resting values during arm exercise in our setup, oxygen transport to the exercising muscles might have been restricted by the inability

of the cardiovascular system to further increase cardiac output. Based on the present findings, improvements in maximal ACE and WCE performance could likely only be expected from enhanced oxygen extraction or by an increase of non-oxidative muscle mass.

ACE versus WCE

The higher workload achieved with ACE is most likely related to the higher mechanical efficiency during ACE compared to WCE.[48,56] During ACE, force can be applied continuously, while during WCE, force is applied only at 20 - 40% of the 360° cycle.[116] Differences in force production, movement pattern and trunk stabilization between WCE and ACE result in a higher metabolic cost for the same workload during WCE. Therefore, ACE might be preferential for outdoor activities involving inclines or to cover long distances.

However, with respect to training, which is generally performed at submaximal workloads, both modes are similar, as no substantial differences in physiological responses or RPE were found, at identical percentages of maximal workload. Accordingly, it could be concluded that ACE and WCE do not differ in their suitability to train the cardiorespiratory system. Nonetheless, the submaximal exercise mode which can be sustained for a longer duration might be more beneficial for the improvement of cardiovascular health.[31,65]

Exercise ventilation

Interestingly, tidal volume remained low in cSCI, while minute ventilation and breathing frequency increased with exercise intensity. Also, compared to AB, cSCI breathed at a lower percentage of their vital capacity, possibly because the diaphragm also acts as a postural muscle in cSCI.[106] Therefore, the smaller tidal volume might reflect a compromise between respiratory needs and maintaining upper body balance. In addition, the small tidal volume

might also result from the limited ability to actively expire, thereby recruiting expiratory reserve volume.

Furthermore, reduced active respiratory muscle mass increases the overall demand on the diaphragm and its susceptibility to fatigue.[15] In AB, exercise-induced diaphragmatic fatigue has been proposed to attenuate blood flow to locomotor muscles as a result of sympathetically mediated vasoconstriction due to the competition for blood flow between respiratory and locomotor muscles.[29,30] It cannot be ruled out that competition for blood flow between respiratory and arm muscles occurred in the present study, thereby affecting exercise performance. However, since sympathetic vasoconstrictor activity cannot be activated from the cardiovascular centers in cSCI,[74] it is unlikely that this mechanism affected exercise performance in this population.

Despite the high demand on the respiratory system in cSCI, evidence that the respiratory system does not limit exercise performance is provided by Taylor *et al.,*[110] who did not observe exercise-induced diaphragmatic fatigue after intensive constant-load arm crank exercise in highly trained cSCI. These authors believe that their findings can be extended to less fit cSCI, since these subjects will be even less able to reach the limits of their breathing capacity.

Technical considerations

A first consideration is that cardiac output determination by the use of Innocor^{TM} in cSCI is new. We tested the reliability of these measurements in separate sessions and obtained coefficients of variation (6.8%) comparable to gold standard methods, which generally lie between 5 - 10%.[125]

Second, our sample size was small, but the inclusion criteria restricted the available number of active and otherwise healthy cSCI. To partly overcome this issue, we included pair-matched AB for comparisons. A sample size of n = 9 is capable of detecting between condition cardiac output differences of 15% of maximal exercise in cSCI with 80% power and 5% alpha error based on the standard deviation of repeated cardiac output measurements on different days.

Third, blood pressure was measured immediately after stopping, rather than during exercise due to movement artifacts. However, we believe that these measurements acceptably reflect pressures during exercise because our values compare well with those assessed during exercise.[71]

Conclusions

By comparing maximal exercise responses of ACE and WCE we could show that these exercise modalities are equivalent with respect to cardiorespiratory stress but seem to be insufficient to elicit adequate volume loading of the heart to maximally stress central hemodynamic mechanisms.[95] Therefore, increases in maximal cardiac output and stroke volume are most likely not to be expected even when including maximal bouts of ACE and WCE in high intensity interval training. Thus, more effective cardiovascular training modes should be considered to enhance cardiovascular health in cSCI.

7. General discussion

By use of innovative technologies, the present work provides a unique insight into determinants of human cardiorespiratory function in response to different training modes. Our findings contribute towards maximizing training efficiency in the future. For instance, the assessment of the operating lung volumes during inspiratory loaded breathing (ILB) emphasizes the importance of imposing and controlling lung volume during ILB-training; i.e. initiating the inspiratory effort after a complete expiration seems to be a critical factor to induce specific rib cage muscle (RCM)-fatigue.

Furthermore, the evaluation of cardiorespiratory responses to arm-crank and wheelchair exercise showed that these exercise modes do not differ in their suitability to train the cardiorespiratory system. However, these training modes do not provide an effective training stimulus to elicit cardiovascular adaptations in cSCI, because stroke volume did not increase in response to exercise in this group.

Inspiratory loaded breathing (ILB) in healthy individuals

Tzelepis *et al.*[114] investigated effects of ILB-training performed at different lung volumes and found that performing ILB from RV results in the greatest increase of respiratory muscle strength. Studies that investigated the effects of ILB-training on exercise performance have provided controversial results. Interestingly, some studies that failed to find improvements in exercise performance seemed not to have imposed the lung volume during ILB.[64,108,128] In contrast, several studies that investigated the effects of ILB-training (residual volume (RV) to total lung capacity (TLC)), showed improvements in exercise performance,[7,99,100,123] potentially supporting the idea of the influence of lung volume during ILB on exercise

outcomes after training. In fact, Romer *et al.*[99] showed that, after ILB-training (performed from RV to TLC), individuals could maintain a higher tidal volume and end-inspiratory volume towards the end of exercise tests, compared to the control group.[99] This is consistent with our observation were RCM-fatigue, and not diaphragmatic fatigue, seemed to impair ventilation during NH. This finding also highlights the importance of respiratory muscle strength, determined predominantly by RCM, during exercise-like ventilation.

Trained respiratory muscles might delay the onset of respiratory muscle fatigue. However, the exact mechanism by which respiratory muscle fatigue influences exercise tolerance is not clear. Potential determinants include changes in respiratory muscle work (efficiency) or central governed consequences (e.g. perception of effort, inhibition of motor output, sympathetic mediated vasoconstriction).[29,81,101]

In practice, maximal inspiratory pressure (MIP) measurements before and after ILB, as used in the present study, would offer a simple method to evaluate the effectiveness of the actual training stimulus. For future research, MIP measurements during the course of ILB combined with continuous recordings of OEP, oesophageal/gastric pressure, and EMG of the respiratory muscles will provide more detailed information of the time-course and muscle involvement during ILB. Furthermore, a controlled ILB-training study (start of inspiratory effort: one group at RV, one group at functional residual volume) comparing the effects of ILB-training on exercise performance would confirm our assumptions if the improvements in exercise performance were higher in the RV group.

Although we could show that lung volume is a critical factor during ILB, a lot remains unknown. Respiratory movements are complex and depend on the relative contribution and

mechanical interaction of many muscles. No data has been obtained on the pressure-generation capacity of isolated respiratory muscles in humans. Thus, the exact interactions and volume dependence between the RCM and the diaphragm are not known.[26] To advance research in this field, attention should be directed towards the development of dynamic simulation models where the combination of different muscles and flow/force parameters can be modulated. Furthermore, human studies using imaging technologies (activation of brain areas, structure of the respiratory muscles), blood flow measurements, and respiratory muscle biopsies (fibre type composition, capillarisation, metabolic activity) might contribute towards clarifying the underlying mechanisms leading to the ergogenic effect of respiratory muscle training.

Hemodynamic responses to exercise

Failure to increase stroke volume in response to arm exercise in individuals with cervical spinal cord injury (cSCI) has important implications for exercise, because low stroke volume can be a limiting factor for a rise in cardiac output, oxygen transport, and exercise capacity.[63] This finding is consistent with previous observations of unchanged stroke volume in response to submaximal exercise in cSCI.[63,84]

The increase of stroke volume in able-bodied individuals (AB) during arm exercise, however, indicates that arm exercise has the potential to elicit central cardiovascular training adaptations. This rise in stroke volume in AB is also seen in the adjustment in blood pressure, while in cSCI the systolic blood pressure did not increase in response to exercise. Exercise hypotension can be a limiting factor for cardiovascular circulation and it would be interesting to investigate, whether compression of the body tissues, for example by use of water

immersion or compression suits, might improve cardiovascular circulation owing to central shifts of intravascular blood volume.

Moreover, exercise in supine position might also improve cardiovascular circulation, since upright posture causes blood to pool in the venous compliance vessels. Consequences of the different exercise conditions on cardiovascular circulation during maximal exercise remains to be determined. If maximal oxygen uptake and exercise performance does not improve despite enhanced cardiovascular circulation, then it would be reasonable to conclude that the exercise limitation in cSCI is located peripherally rather than centrally.[62]

Over the past years, exercise based on functional electrical stimulation has emerged. Functional electrical stimulation recruits a larger muscle mass and activates the muscle pump in the lower extremities, which in turn enhances venous return and stroke volume.[40,59] Unfortunately, functional electrical stimulation training needs technical assistance and is time and cost intensive, therefore integrating functional electrical stimulation in training routines has proven difficult.

Arm-crank or wheelchair exercise?

Since arm-crank and wheelchair exercise are conventional exercise modes in cSCI, it is of interest to know which one of the two modes should be recommended for training. The data obtained in our study indicates, that arm-crank and wheelchair exercise do not differ in their suitability to train the cardiorespiratory system, having similar cardiorespiratory responses and RPE. However, the exercise type that could be sustained for a longer duration, for example, at 70 - 80% of the maximum, has the greater potential to improve cardiovascular health. Moreover, high intensity arm training (70 - 80% of the heart rate reserve)[22] in SCI

suggests that improvements in physical capacity and blood lipid profile were more pronounced compared to low intensity training.

Another consideration, which is relevant with regard to overuse and pain,[34] is that the mechanical load on the shoulder joint during arm-crank and wheelchair exercise is different. However, since hand-rim propulsion in cSCI is anyway often used for locomotion in daily life, arm-crank ergometery training might contribute towards diminishing the risk of overuse and offers variation considering the usual movement pattern. Moreover, since cardiovascular training stimulus of arm-crank and wheelchair exercise has been found to be comparable, these exercise types can be used interchangeably without loss of training effect.

Respiratory muscle training in cSCI?

Respiration in cSCI is compromised by the reduced active respiratory muscle mass and chest wall stiffness can lead to increased breathing work.[130] In addition, respiratory muscles in cSCI are recruited for multiple purposes, including respiration, postural support, and arm work.[17,77] Obviously, ILB offers an attractive, affordable, and shoulder joint friendly alternative to arm exercise and might improve respiratory function and/or exercise performance. Although a literature review[14] could not confirm a beneficial effect of ILB-training on respiratory function in SCI, this outcome might be judged with caution since the authors acknowledge that the small number of studies do not allow firm conclusions. Moreover, a beneficial effect of respiratory muscle training on exercise performance cannot be excluded since this question was not addressed in the above mentioned review.

It should be noted that our findings regarding the recommended range of breathing (RV - TLC) during ILB need further evaluation in cSCI, since low active muscle mass of the chest wall and sitting position might alter respiratory mechanics.

The loss of major active expiratory muscles in cSCI results in weak coughing,[15] Normocapnic hyperpnea (NH)-training might therefore be advantageous compared to ILB, because NH involves active expiration. Sufficient data to determine the effects of NH in cSCI is not yet available.[117]

Interactions between the respiratory and cardiovascular systems

Respiratory mechanics affect blood circulation in different ways. Recently, Aliverti *et al.*[5] reported that simultaneous contraction of the diaphragm and abdominal muscles during an expulsive maneuver can shift blood from the splanchnic circulation to the extremities. Moreover, expiratory loading (increasing intraabdominal pressure)[109] or smaller thoracic excursion[50,86] led to a decrease in stroke volume. However, with regard to our research, the main question is: Does stroke volume increase during ILB or NH in cSCI? If yes, then respiratory muscle training would offer the ideal training mode to improve cardiac fitness in this population. While in AB, stroke volume does not change in response to acute ILB or NH[19,121,122] or after NH-training,[80] the effect of ILB or NH on cardiovascular circulation in cSCI is still unknown. Thus it remains to be investigated whether arm exercise or some type of respiratory muscle training will provide larger gains in cardiovascular fitness in cSCI.

Summary of findings

Our findings demonstrate that respiratory muscle fatigue depends on the lung volume from which inspiratory efforts are made during IRB. To optimize IRB-training, breaths should be initiated from residual volume.

We found non-invasive cardiac output measurements using Innocor^{TM} to be as reliable in cSCI as they are in AB. Consequently, Innocor^{TM} can be recommended for repeated assessments of cardiac output in cSCI within routine diagnostics or for evaluation of training progress.

The lower cardiac output in cSCI compared to AB at equivalent workloads reflects the inability of the circulatory system to increase stroke volume and is most likely associated with the disturbed sympathetic nervous system in cSCI.

Cardiorespiratory parameters and ratings of perceived exertion in response to maximal arm-crank and wheelchair exercise were similar in cSCI, despite higher maximal power output with arm-crank exercise. Thus, both exercise modes seem equally suited for cardiorespiratory training while arm-crank exercise is more efficient with respect to power output and might therefore be preferential for outdoor activities.

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9. Abbreviations

AB	able-bodied individuals
ACE	arm-crank exercise
C	cervical vertebra
CO	cardiac output
cSCI	individuals with cervical spinal cord injury
CV	coefficient of variation
EE	end-expiratory
EEV	end-expiratory volume
EI	end-inspiratory
EIV	end-inspiratory volume
FEV_1	forced expiratory volume in 1 s
FIV_1	forced inspiratory volume in 1 s
f_R	breathing frequency
FRC	functional residual capacity
FVC	forced vital capacity
HR	heart rate
ICC	intra- and interclass correlation coefficient
ILB	inspiratory loaded breathing
LF	lung function
L_a	blood lactate concentration
LOA	limits of agreement
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure

MVV	maximal voluntary ventilation
NH	normocapnic hyperpnea
OEP	optoelectronic plethysmography
PEF	peak expiratory flow
PIF	peak inspiratory flow
QB	quiet breathing
R	rest
RCM	rib cage muscles
RPE	ratings of perceived exertion
rpm	rounds per minute
RV	residual volume
SD	standard deviation
SE	standard error
SNIP	sniff nasal inspiratory pressure
SpO_2	arterial oxygen saturation
SV	stroke volume
TLC	total lung capacity
VC	vital capacity
$\dot{V}_E$	minute ventilation
V_T	tidal volume
$\dot{V}O_2$	oxygen consumption
WCE	wheelchair exercise
zQL	Personen mit zervikaler Querschnittlähmung

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11. Curriculum vitae

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