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Mattias Hill

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 15th of December at 09.00 in Segerfalksalen, BMC, Sölvegatan 17, Lund

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Title: Cardiopulmonary Health in Middle-aged People with Long-term Cervical and Upper Thoracic Spinal Cord Injuries

Abstract: Life expectancy in people with spinal cord injury (SCI) is lower than the general population as cardiovascular and respiratory diseases occur prematurely. Life expectancy is related to SCI severity i.e., it is reduced in relation to a more rostral neurological level of injury (NLI) and greater severity grade based on American Spinal Injury Association Impairment scale (AIS). Improvement of long-term mortality is paramount to increase life expectancy. However, knowledge of cardiopulmonary health in people with SCI many years after injury is very limited.

The overarching aim of this thesis was to describe and explore cardiopulmonary health in middle-aged people with long-term cervical and upper thoracic SCI in the Skåne region, Sweden, and to compare the results with matched controls from the general population.

The first study in this thesis describes the cohort of the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment (SPICA) and subsequent three studies explore cardiopulmonary function and structure comprehensively.

The thesis is based on subsets of data from SPICA. The 25 participants (20% women, NLI C2-T6 and AIS A-C) in SPICA had a mean age of 58 years and mean time since injury of 28 years. Non-SCI matched control data were obtained from the Swedish CArdioPulmonary bioImage Study (SCAPIS).

Characteristics of the SPICA cohort (Study I) do not stand out in relation to previous SCI research. Nearly three quarters of the participants were classified as having a high cardiovascular disease risk. Overall, the cardiopulmonary results (Study II-IV) demonstrate cardiopulmonary functional impairments compared to controls. Several of the cardiopulmonary functional impairments were worse with a more rostral NLI. In the participants compared to controls, cardiopulmonary structure was not considerably different, for one variable significantly better (intima media thickness of the carotid bulb), and cholesterol levels were significantly lower. Linear scars of atelectasis were significantly associated with increasing age among the participants with SCI.

In conclusion, cardiopulmonary health is generally worse in middle-aged people with cervical and upper thoracic SCI as compared to the general population. There are a few noteworthy exceptions. Lower cholesterol levels may be a significant protective factor for the development of atherosclerosis and an explanation why the atherosclerotic burden was not increased in this population. The cardiopulmonary comorbidities and characteristics in combination with cardiopulmonary impairments reveal several factors implicating an increased vulnerability for cardiopulmonary complications irrespective of structural impairments. Age-related presence of linear scars of atelectasis in this population may indicate loss of elastic recoil and a specific vulnerability for pulmonary complications. Future research needs to confirm these results, determine the pathophysiological mechanism of cardiopulmonary impairments, and understand the clinical significance of these findings in terms of prognosis and preventive strategies.

Key words: Autonomic Nervous System Diseases, Cardiovascular Diseases, Respiratory Tract Diseases, Spinal Cord Injuries

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Abstract

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List of Papers

Paper I

Hill M, Jörgensen S, Engström G, Persson M, Lexell J. The Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment (SPICA): Methodology, Cohort Demographics and Initial Results. American Journal of Physical Medicine & Rehabilitation. 2020;99:522-531.

Paper II

Hill M, Jörgensen S, Engström G, Persson M, Platonov P, Hamrefors V, Lexell J. Cardiovascular Autonomic Function in Middle-aged People with Long-term Cervical and Upper Thoracic Spinal Cord Injuries (unpublished manuscript).

Paper III

Hill M, Jörgensen S, Engström G, Persson M, Lexell J. Coronary and Carotid Imaging of Atherosclerosis and Contributing Factors in Middle-aged People with Long-term Cervical and Upper Thoracic Spinal Cord Injuries (published online ahead of print). PM&R, the journal of injury, functioning and rehabilitation. 2023;10.1002/pmrj.13043.

Paper IV

Hill M, Jörgensen S, Engström G, Persson M, Wollmer P, Lexell J. Functional and structural impairments of the pulmonary system in middle-aged people with cervical and upper thoracic spinal cord injuries. Journal of Spinal Cord Medicine. 2023;46:732-741.

Abbreviations

ABPM	Ambulatory 24 hrs blood pressure
AD	Autonomic dysreflexia
ADFSCI	Autonomic dysfunction following spinal cord injury[1]
AIS	American Spinal Injury Association Impairment Scale[2]
AV	Atrioventricular
BMI	Body mass index
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CRP	C-reactive protein
CRPD	Convention on the Rights of Persons with Disabilities
CT	Computed tomography
CVD	Cardiovascular disease
DBT	Deep breathing test
D_{LCO}	Diffusing capacity of the lungs for carbon monoxide
E-I	Expiration–inspiration difference
E/I	Expiration–inspiration ratio
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
Fres	Resonant frequency
FVC	Forced vital capacity
HF	High frequency
HRV	Heart rate variability
IMT	Intima media thickness
IOS	Impulse oscillometry
ISNCSCI	International standards for the neurological classification of spinal cord injury[2]
k_{CO}	Carbon monoxide transfer coefficient

LF	Low frequency
MCR	Mean circular resultant
MEF_{50}	Maximal expiratory flow at 50%
NLI	Neurological level of injury[2]
OR	Odds ratio
RMSSD	Root mean square of successive differences
SA	Sinoatrial
SCAPIS	Swedish CArdioPulmonary bioImage Study[3]
SCORE	Systematic coronary risk evaluation
SCI	Spinal cord injury
SDNN	Standard deviation of the normal-to-normal interval
SHC	Secondary health condition
SPICA	Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment
V_A	Alveolar volume
WC	Waist circumference

Definitions

AIS A[2]	A complete spinal cord injury, i.e., no sensory or motor function is preserved in the S4–S5-segments
AIS B[2]	A sensory incomplete spinal cord injury, i.e., preserved functions in the S4–S5-segments; sensory but not motor function is preserved below the NLI and motor function is not preserved more than three levels below the motor level on either body half
AIS C[2]	A motor incomplete spinal cord injury, i.e., motor functions are preserved below the NLI; the degree of motor function is 0-2 in a majority of the key muscles
AIS D[2]	A motor incomplete spinal cord injury, i.e., motor functions are preserved below the NLI; the degree of motor function is 3-5 in a majority of the key muscles
AIS E[2]	A spinal cord injury with full recovery in all segments from previous verified deficits
Any structural impairment	Presence of any pulmonary structural impairments
AX[4]	The quantitative index between 5 Hz and the resonant frequency of the total respiratory reactance
Bronchial wall thickening[5]	Presence of abnormal bronchial wall thickening
Bronchiectasis[5]	Presence of dilatated bronchi with respect to the pulmonary artery, no tapering of bronchi and bronchi should be identified within 1 cm of the pleural surface
Consolidation[5]	Presence of homogenous increase in the pulmonary parenchyma obscuring airway walls and vessels margins
Coronary artery calcium[6]	Coronary artery calcium lesions defined as at least in three neighbouring pixels in a volume of 1 mm^3 the calcium threshold of 130 HU is exceeded
Coronary artery calcium score[6]	Calculation of a score according to Agatston: the area of calcification of each 3-mm slice is multiplied with an intensity factor and summed across slices for the whole coronary artery tree

Coronary plaque[7]	Presence of a structure, clearly distinguished from the lumen and surrounding pericardial tissue, located within and/or adjacent to the vessel lumen
Lung cysts[5]	Presence of a round area with well-defined interface with normal lung appearing low-attenuated or lucent
Diastolic blood pressure	The pressure of the arterial walls in between heart beats
Dipper[8]	10%-20% nocturnal systolic blood pressure fall
D_{LCO}[9]	The total CO uptake by the lung per unit of time per unit CO driving pressure
E-I[10]	Heart rate difference between expiration and inspiration
Emphysema[5]	Presence of low-attenuating focal areas
Extreme-dipper[8]	>20% nocturnal systolic blood pressure fall
FEV_1[11]	The volume of air exhaled during the first second of the FVC measure
FEV_1/FVC[11]	FEV_1 to FVC ratio
FVC[11]	Vital capacity measure is performed with a maximally forced and complete inspiration/expiration
Ground glass[5]	Presence of an area of hazy increased opacity of lung where bronchial and vascular margins are preserved
Heart rate	Heart beats per minute
Heart rate variability[12]	The HRV is the changes in the time intervals occurring between consecutive heartbeats. HRV can be measured by different methods. Commonly used methods are time domain and frequency domain methods. Time domain measures are evaluating the amount of variance of the changes in the time intervals. Frequency domain measures are evaluating the amount of power in different frequency band (high, low, very low and ultralow frequencies). These oscillations of the heart rhythm tend to correlate to different physiological phenomenon.
HF[12]	A frequency domain HRV measure assessing the power in high frequency range (0.15-0.4 Hz) reflecting

	parasympathetic activity and corresponding to respiratory cycle-related heart rate variations
Honeycombing[5]	Presence of cystic air spaces, which appear in clusters with well-defined walls
Intima media thickness[13]	The thickness between the intima-lumen interface and media-adventitia interface
ISNCSCI[2]	Clinical examination assessing the neurological level of injury and the degree of injury according to the AIS
k_{CO}[9]	The fall in alveolar CO concentration per unit CO driving pressure
LF[12]	The power in low frequency range (0.04-0.15 Hz) measuring mainly cardiac parasympathetic and sympathetic activity, but also other factors, such as the renin-angiotensin-aldosterone system
LF/HF[12]	The LF/HF ratio suggested to be a measure of the balance between cardiac sympathetic (LF) and parasympathetic (HF) activity
Linear scars of atelectasis[5]	Presence of regions appearing with a patchwork of differing attenuation
Lymphadenopathy[5]	Presence of enlarged hilar or mediastinal lymph node
MCR[10]	A vector-based HRV measure reducing the effects of differences between individuals in mean heart rate and premature ventricular contractions
MEF_{50}[11]	The maximal forced expiratory flow after 50% of the FVC has been exhaled
Middle age[14]	The age range between 45 and 65 years preceding old age
Mosaic attenuation[5]	Presence of reduced volume and increased attenuation with a linear configuration and a subsegmental distribution
NLI[2]	Neurological level of injury defined as the most caudal segment of the spinal cord with preserved sensory and motor functions
Non-dipper[8]	0-10% nocturnal systolic blood pressure fall

Orthostatic blood pressure[8]	The blood pressure difference from a resting supine position and three minutes after rising up to a seated or standing position
Plaque (carotid)[13]	Presence of a focal widening relative to adjacent segments with protrusion into the vessel lumen at least 0.5 mm or 50% of the surrounding IMT value, or a thickness between the intima-lumen interface and media-adventitia interface exceeding 1.5 mm
Plaque size (carotid)[13]	The cross-sectional area of longitudinal views of the plaque
R20[4]	The respiratory resistance measured at 20 Hz, including mainly central airway resistance and to a lesser extent peripheral airways, lung tissue and chest wall resistance
R5[4]	The respiratory resistance measured at 5 Hz including central and peripheral airways, lung tissue and chest wall resistance
R5-R20[4]	The respiratory resistance measured at 5 Hz minus the resistance measured at 20 Hz, indicating the resistance of the small airways
Resonant frequency[4]	The frequency at which elastance and inertance are equal, i.e., the shift from passive tension (inertive forces) to active stretch (reflecting elastance) of the lung tissue in response to the pressure wave force
Respiratory impedance[4]	Calculations of the resistance and reactance of the pulmonary system from the total force needed to propagate a pressure wave through the airways
Respiratory reactance[4]	The energy generated from the elastic recoil of the lungs after distension by the pressure wave. Comprises inertance and elastance. Inertance are inertive forces of the moving air column in the airways and elastance reflecting the elastic properties of the pulmonary system.
Respiratory resistance[4]	Energy required to propagate a pressure wave through the airways, i.e., propagating through the bronchi and bronchioles, and distending the parenchyma
Reticular abnormality[5]	Presence of a collection of small linear opacities resembling a net constituted by interlobular septal

	thickening, cyst walls of honeycombing or intralobular lines
Reverse-dipper[8]	Nocturnal systolic blood pressure rise
RMSSD[12]	The root mean square of successive differences is used to estimate changes in HRV mediated from parasympathetic activity and reflects the beat-to-beat variance in heart rate: measures are obtained by calculating time differences between successive heartbeats, then each value is squared and averaged, and finally the square root of the total is calculated
SD_{BP}	The standard deviation of the ambulatory 24 hrs blood pressure measurements
SD_{HR}	The standard deviation of the heart rate
SDNN[12]	The standard deviation of the normal-to-normal interval (i.e., all intervals between adjacent normal QRS complexes) both parasympathetic and sympathetic activity contribute to SDNN
Segment involvement score[7]	The sum of coronary artery segments with plaques
Slow vital capacity[11]	Vital capacity measure is performed with an unforced and complete expiration
Solid nodules[5]	Presence of an irregular or rounded opacity measuring up to 3 cm in diameter with a homogenous attenuation
Systolic blood pressure	The pressure of the arterial walls during the heartbeat
V_A[9]	The alveolar volume measured by gas dilution
Vital capacity[11]	The change in volume between full inspiration and complete expiration
X5[4]	The respiratory reactance at 5 Hz, incorporating the mass-inertive forces of the moving air column (inertance) and the elastic properties of lung periphery (elastance)

Preface

I was mainly working at a department of internal medicine during my initial years as an intern after medical school and as a licensed physician. I found practising medicine, to diagnose and treat various conditions exciting. However, I was troubled by feelings of shortcomings of the health care's approach to patients. I experienced that the focus was on medical diagnosis and managing the inpatient hospital beds, pushing aside the space to meet the patient and the relatives in their current situation. I had doubts trying to figure out my future professional direction. At that time, I noticed a job advertisement of a residency in rehabilitation medicine at Skåne University Hospital. I was clearly unaware of the specialty and the characteristics of the working methods. After some research I became really interested as rehabilitation medicine seemed to correspond to my aspirations. I applied and got the job.

I began my residency in rehabilitation medicine in 2015 and I was not disappointed. This was something else, wherein the person-centered perspective was the very core of the specialty. In the spinal cord injury (SCI) unit I realised that SCI is a multifaceted condition with several implications for internal medicine. This was exciting as it was linking together my previous experiences. When the head of our department gave me a tip on a large research project that might be of interest my research aspirations took off.

The research project was the Swedish CArdioPulmonary bioImage Study (SCAPIS) of which the broad and in-depth baseline data collection of cardiopulmonary assessments was in progress. I contacted my colleague, who was also a final year PhD student and would later become my assistant supervisor, if she thought that our professor would be interested in an idea to collaborate with the SCAPIS to collect data also in people with SCI. Yes, he was! However, we were in a hurry to apply for ethical permission as the data collection of SCAPIS was running out of time. Luckily, our first application, at the latest possible local ethical review board meeting, was approved! We could start recruiting participants, and even before I was admitted as a PhD student in April 2018 almost all the data collection was completed.

Looking back now when writing my thesis, the basis of it was really a close call. Now I have developed so many skills in the rather narrow research area of this thesis, and the generic knowledge and skills of the doctoral programme, such as pedagogical experiences. These acquired skills, providing reflective material on the clinical work, I believe have had even more influence on my professional development as a specialist in rehabilitation medicine than the clinical activities alone. Accordingly, I am now well-prepared to face the challenges of academic as well as clinical work when I pursue my future professional directions.

Context of this thesis

This thesis was carried out within the Rehabilitation Medicine Research Group, Faculty of Medicine, the Department of Rehabilitation Medicine, Skåne University Hospital and through collaboration with the Malmö study site of the Swedish CardioPulmonary bioImage Study (SCAPIS), Skåne University Hospital at the Clinical Research Centre, Lund University, Malmö.

In 2017, the idea to collaborate with a state-of-the-art multicentre study (SCAPIS) to collect data in a cohort of people with SCI and obtain control data from SCAPIS was conceptualized by me. The project was named the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment with the acronym SPICA. A study protocol, based on the SCAPIS baseline protocol was designed together with my main supervisor professor Jan Lexell and assistant supervisor Sophie Jörgensen. SPICA is a cross-sectional study of middle-aged people with long-term cervical and upper thoracic spinal cord injuries with matched controls. I wrote the application to the Regional Ethical Review Board with support from my future supervisors.

After the approval of the ethical application, I recruited all the participants with SCI. The data collection at SCAPIS in Malmö involved three separate study visits and numerous different assessments for each participant, and I was participating in all the data collection. During the study visits I gave the participants oral information and, after all study visits were completed, a written summary of their findings. If there were medical issues, I addressed these. Given this close interaction with the participants during and after the data collection I got invaluable insights into the everyday life of people who have lived with a major disability for on average three decades.

Thereafter my doctoral studies began in April 2018. I created the database of the project and applied for control data from SCAPIS. I also wrote funding applications which were very successful, one being a 4-year PhD-grant from the Promobilia Foundation. During my doctoral studies, I formulated the specific research questions, managed contacts for further analyses of the raw data, if necessary, conducted the data analyses and wrote the manuscripts for the four papers included in this thesis. All in close collaboration with my supervisors and co-authors.

This thesis is based on the data collection of SPICA and provides a unique and detailed cross-sectional clinical picture of cardiopulmonary health in middle-aged people with long-term cervical and upper thoracic SCI in the Skåne region, Sweden. In addition, detailed comparison with matched controls from the general population has been performed. The results from the studies of this thesis provide directions for future research efforts.

Introduction

Spinal cord injury (SCI) can have a substantial impact on body functions due to neurological deficits, which influence longevity negatively.[15] Following the Second World War, the comprehensive approach of SCI care at Stoke Mandeville Hospital, England was established by the work of Sir Ludwig Guttmann.[16] This led to a remarkable reduction in the extremely high first-year mortality.[16,17] Thereby, Guttmann and his colleagues lay the foundation for the development of the standards of SCI care and the improvement of survival and longevity in people with SCI that occurred during the 20th century.[18]

These advances in SCI care led to a growing population of people aging with SCI.[19] However, the continuous improvements in longevity have abated, and while the general population continues to live longer, that is not the case for people with SCI.[18] Among these, people with a high SCI, i.e., cervical and upper thoracic, have the lowest life expectancy.[15] Although diseases of the cardiovascular and pulmonary systems are the major causes of death in SCI[20,21] little is known about cardiopulmonary health in people who have lived many years with their injury.

The four papers comprising this thesis describe and explore cardiopulmonary health in middle-aged people with long-term cervical and upper thoracic SCI in the Skåne region, Sweden. The findings are compared with the general population. Such an in-depth and broad assessment has not been performed previously and especially not in this vulnerable SCI population. The purpose is primarily to increase our knowledge, generate hypotheses to direct future research and provide a detailed clinical picture of cardiopulmonary health in this population. Thereby, this thesis contributes to the development of the standards of SCI care to improve longevity in SCI in the longer term.

Spinal cord injury

The spinal cord serves as a large conduit for the transmission of nerve signals between the brain and the peripheral nervous system including sensory, motor and autonomic transmission.[2] In addition, the spinal cord has independent body functions such as coordinating spinal reflexes.[22,23] The spinal cord is organized with longitudinally oriented white matter (spinal tracts) surrounding the centrally oriented grey matter.[2] The grey matter is segmentally organized and contains most

of the spinal neuronal cell bodies.[2] There are 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 0-2 coccygeal segments.[2] From these segments corresponding spinal nerves are emerging, carrying sensory, motor and autonomic nerve signals between the spinal cord and the body.[2] In Figure 1, the organization and the representation of body functions according to these segments are depicted.

SCI affects the conduction of nerve signals across the lesion.[2] International Standards for the Neurological Classification of SCI (ISNCSCI) has been developed to systematically examine sensorimotor impairments following SCI.[2] The examination takes into account both involved segments to determine the neurological level of injury (NLI) and injury severity according to the American Spinal Injury Association Impairment Scale (AIS).[2] These variables of the ISNCSCI are described in Table 1.

Cervical NLI causes tetraplegia (impairments affecting all four limbs), whereas a lower NLI causes paraplegia (impairments affecting only the lower limbs).[2] The ISNCSCI is widely used to document remaining sensorimotor functions both in the scientific and clinical setting. ISNCSCI does not assess autonomic impairments. Therefore, the International Standards to document remaining Autonomic Function after SCI (ISAFSCI) was developed to be used in conjunction with the ISNCSCI.[24] However, these standards are more frequently used as a part of the clinical evaluation and not in SCI research.

SCI is a heterogeneous condition. Classified on the sensorimotor impairments alone, not considering the autonomic impairments affecting the body organs, the 28 different NLI and the four varying degrees of impairments result in 112 possible combinations, where cervical NLI are most frequently occurring.[18,25] In addition, both AIS C, and especially AIS D, are heterogeneous within the category with varying degree of sensorimotor function deficits.[2]

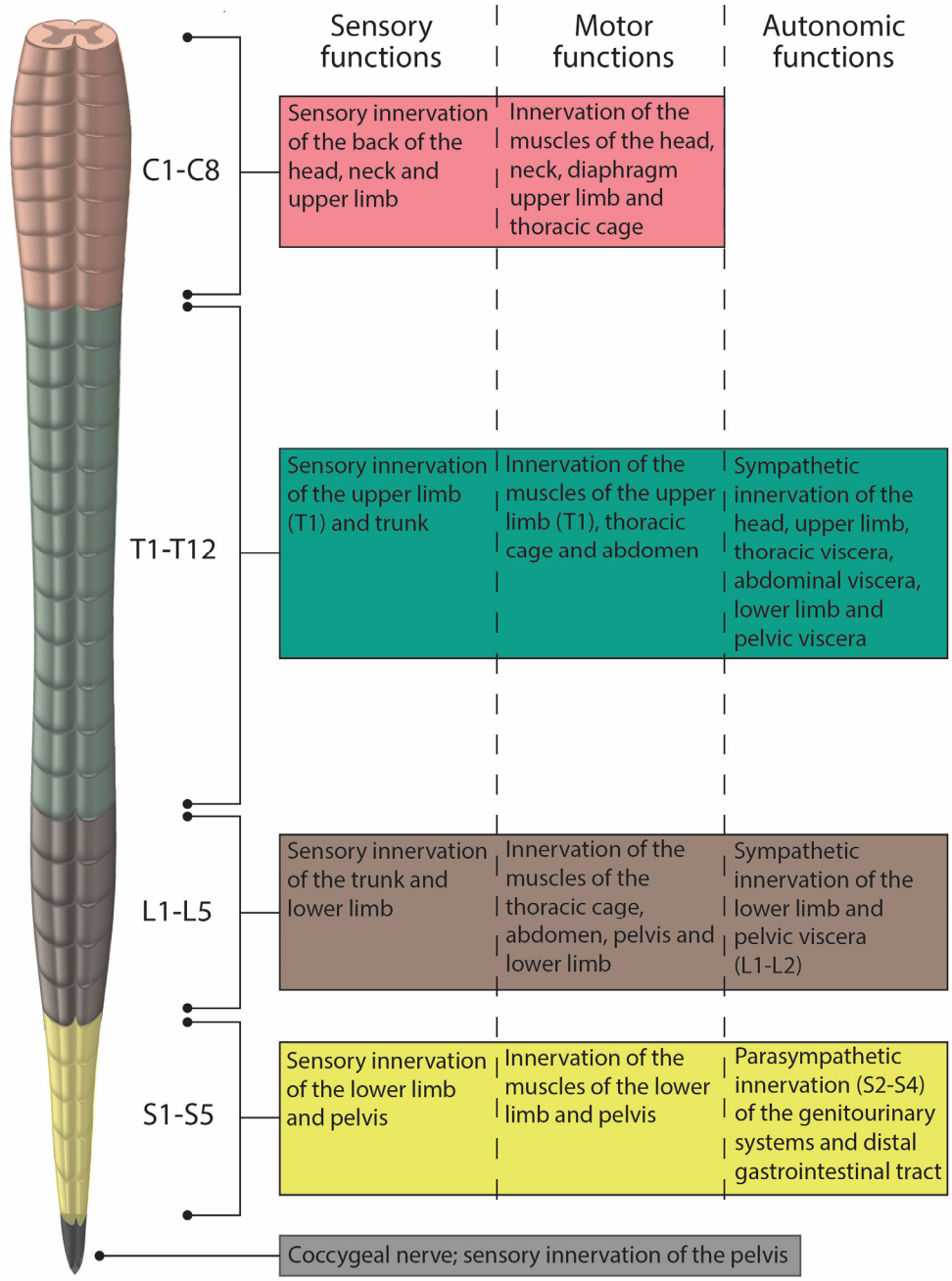


Figure 1. Schematic diagram of the segmental organization of the spinal cord and the representation of body functions[2,24]

C=cervical segments; L=lumbar segments; S=sacral segments; T=thoracic segments

Table 1. Neurological level of injury and ASIA Impairment scale according to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI)[2]

Classification	
Neurological level of injury	The NLI is the most caudal segment of the spinal cord with preserved sensory and motor functions
Sensory level	Bilateral examination of key sensory points according to 28 dermatomes determing the sensory level, i.e., the most caudal segment with normal sensory functions for both body halfs
Motor level	Bilateral examination of key muscles according to ten myotomes to determine the motor level
Degree of impairment	The completeness of sensory and motor impairments according to the American Spinal Injury Association (ASIA) injury scale (AIS)
AIS A	A complete injury, i.e., no sensory or motor function is preserved in the S4-S5-segments
AIS B	A sensory incomplete injury, i.e., preserved functions in the S4-S5-segments; sensory but not motor function is preserved below the NLI and motor function is not preserved more than three levels below the motor level on either body half
AIS C	A motor incomplete injury, i.e., motor functions are preserved below the NLI; the degree of motor function is 0-2[1] in a majority of the key muscles
AIS D	A motor incomplete injury, i.e., motor functions are preserved below the NLI; the degree of motor function is 3-5[1] in a majority of the key muscles
AIS E	A normal injury, i.e., full recovery in all segments from previous verified deficits

ASIA= American Spinal Injury Association; NLI= neurological level of injury

[1]Degree of muscle function is graded on a six-point scale from 0=no muscle function to 5=normal and 3 means full active range of motion against gravity

Epidemiology

The origin of the SCI can be either traumatic or non-traumatic. Among the most common causes of traumatic SCI are motor vehicle accidents, falls, acts of violence and sports injuries.[18,25] Non-traumatic SCI can be caused by several different conditions such as tumours, spinal cord infarctions and infections.[26]

The incidence rates of traumatic SCI in the Western World vary.[18,25] The highest incidence rates are in the US with on average 40 cases per million population (not population-based and thus lower than the true rate).[18] Historically, traumatic SCI occurred predominantly in younger men.[18] During recent decades, there has been a shift towards a middle-aged population and the incidence in men and women is getting more even.[18] In Sweden, about 250-300 people sustain a SCI annually, which means an incidence rate of 24-29 cases per million population.[27] In 2018, 65% were men, 40% were non-traumatic and only 22% were younger than 45 years.[27] The

most common traumatic aetiology was falls (48%); a majority had a cervical NLI (57%) and AIS D (59%).[27]

During the 20th century, the all-cause SCI mortality was greatly reduced following advances in acute management and rehabilitation.[18] The mortality is still higher than in the general population and standardized mortality rates in SCI have been reported to be 1.5 to 5 times higher as compared to the general population.[15,28] NLI and degree of impairment are the most important predictors, i.e., increased mortality with a more rostral NLI and greater completeness of SCI.[15,18,25] In the study by Middleton et al.[29] reporting life expectancy from 25 to 65 years, the authors demonstrated a strong relation to the extent of neurological impairment. Overall, 40-year survival rates were 47% and 62% for first-year survivors with tetraplegia and paraplegia, respectively.[29] Life expectancies from 25 to 65 years in people with AIS A-C were reported to be 64-69% for C1-C4, 65-74% for C5-C8, 88-91% for paraplegia, and 96-97% for all people with AIS D, respectively.[29]

The reduced mortality has led to a continuously increased prevalence and, thus, a growing population of people aging with SCI.[18] However, no meaningful improvement in life expectancy has occurred in recent decades.[18] During the same period reductions in all-cause mortality caused an increase in life expectancy in the general population.[30] Therefore, life expectancy in the SCI population has been relatively reduced compared with the general population.[18] Despite this feature, which indicate to target the long-term mortality in SCI,[18] the understanding of cardiopulmonary health in long-term SCI is limited. Therefore, there is a need to improve our knowledge of cardiopulmonary health in people with SCI many years after injury.

Rehabilitation

The multifaceted nature of SCI, potentially affecting all body organs, primarily or secondarily, results in varying degrees of disability. This requires a specialized rehabilitation team from a SCI unit, as soon as possible, after injury to reduce complications and mortality.[31]

After initial stabilization, the focus shifts towards a goal-oriented rehabilitation process.[32] This process consists of: (1) continuous *assessment* of the condition from a biopsychosocial perspective according to the International Classification of Functioning, Disability and Health (ICF);[33] (2) *goal setting*; (3) different *actions* to attain the goals; and (4) appropriate *evaluation* of the goal attainment following these actions.[32]

The core of the rehabilitation process is an interdisciplinary team approach.[32] Interdisciplinary teams consist of professions from different disciplines together with the people with SCI and their close relatives.[32] The various disciplines of the rehabilitation team can be physicians, nurses, assistant nurses, occupational

therapists, physiotherapists, social workers, psychologists, recreational therapists and peer mentors (i.e., a person with lived experience of SCI working at the SCI unit).[32] The team is also closely collaborating with other medical disciplines, the community, employers and others.

The rehabilitation process is carried out in collaboration with the team members to perform all the above-mentioned steps in the process in order to achieve the highest rehabilitation outcome, i.e., "to enable people with disabilities to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels" (World Health Organization).[34]

Lifelong clinical management

After completion of the rehabilitation process, at the point when the goals have been reached, the multifaceted condition requires lifelong follow-up from a team specialized in SCI to assess emerging complications, for example pressure injuries and bowel and bladder management.[35] At the SCI unit at Skåne University Hospital, where the participants in this thesis were recruited, people with SCI are enrolled in a follow-up program. The follow-up frequency is based on the specific needs of the person.

Secondary health conditions

In the follow-up program, the evaluation of secondary health conditions (SHCs) is performed. SHCs are physical, mental, and emotional conditions, which are directly or indirectly influenced by the presence of impairments.[36] Self-management of the SHCs are an important part of the rehabilitation process and in the follow-up. There are several SHCs in SCI due to the effects on different organ systems.[36] Examples of SHCs are neurogenic bladder and bowel dysfunction, long-standing pain, spasticity and osteoporosis.[37-41] In this thesis the focus is on cardiopulmonary SHCs.

Cardiopulmonary health in long-term spinal cord injury

In people with cervical and upper thoracic SCI, there may be severe impairments of cardiopulmonary functions.[42,43] Diseases in these organ systems are the two major causes of death in the aging SCI population.[20,21] Thus, there is a need for increased knowledge of cardiopulmonary health in this population. Cardiopulmonary physiology is described in the following section to understand how the neurological functional impairments after SCI affect the cardiopulmonary system and the different methods of the studies in this thesis assessing different cardiopulmonary body functions. The following section describes the physiology and then SCI-related pathophysiology and diseases (SHCs) of the cardiopulmonary systems in people with SCI many years after their injury.

Cardiovascular autonomic regulation

The cardiovascular system is coordinated by the autonomic nervous system which, in turn, is under the control of supraspinal structures.[44] The parasympathetic nervous system activity to control the heart originates from the brain stem and is transmitted via the vagus nerve.[44] The sympathetic nervous system input to control the heart originates from the spinal cord segments T1-T5.[45] The blood vessels exclusively receive SNS input (segments T1-L2).[45]

The heart's rhythmic contractions are automatic.[46] These are generated from the sinoatrial (SA) node located in the upper right atrium, which generates electrical impulses and atrial contractions.[46] The impulses propagate to the atrioventricular (AV) node located in the lower right atrium.[44] The AV node conducts the electrical impulses through the Purkinje fibers, which generate ventricular contractions.[45] These structures are under the influence of autonomic activity and hormones to coordinate the heart rate, rhythm and contractility (force).[44-47]

Parasympathetic activity acts mostly on the SA and AV nodes, whereas the cardiac sympathetic input terminates at the SA and AV nodes as well as the atria, ventricles and conducting tissue.[44] The two divisions of the autonomic nervous system have opposing effects – parasympathetic activity reduces HR and contractility, sympathetic activity increases HR and contractility.[44]

Blood pressure regulation is exerted by several autonomic actions on the cardiovascular and renal systems.[44,47] The cardiac parasympathetic activity causes lower HR which decreases the cardiac output (stroke volume x heart rate) and thereby blood pressure.[44,48] The sympathetic cardiac activity elevates blood pressure by the augmentation of heart rate and/or the contractility of the heart resulting in a higher cardiac output.[47] Furthermore, the sympathetic activity, acting on the resistance arteries and the venous capacitance vessels, constricts the vessels and elevates blood pressure due to increased total peripheral resistance and reduced vascular capacitance (increase of venous return which in turn increases stroke volume and thus cardiac output), respectively.[47,48]

Sensory information is needed for supraspinal control structures to exert the short-term regulation of blood pressure through autonomic activity. Baroreceptors are stretch-sensitive receptors, which monitor pressure changes in the carotid sinuses and aortic arch.[44] The sensory information is conveyed to the brain stem via the glossopharyngeal nerve and the vagus nerve.[44]

Finally, renal sympathetic activity elevates blood pressure as the pressure natriuresis mechanism is shifted to higher pressures to maintain homeostasis.[47,49] This shift is due to renin release, activating the renin-angiotensin-aldosterone-system.[47] The renal regulation exerts the most important effects on the long-term level of blood pressure, whereas the cardiovascular regulation exerts short-term effects.[49]

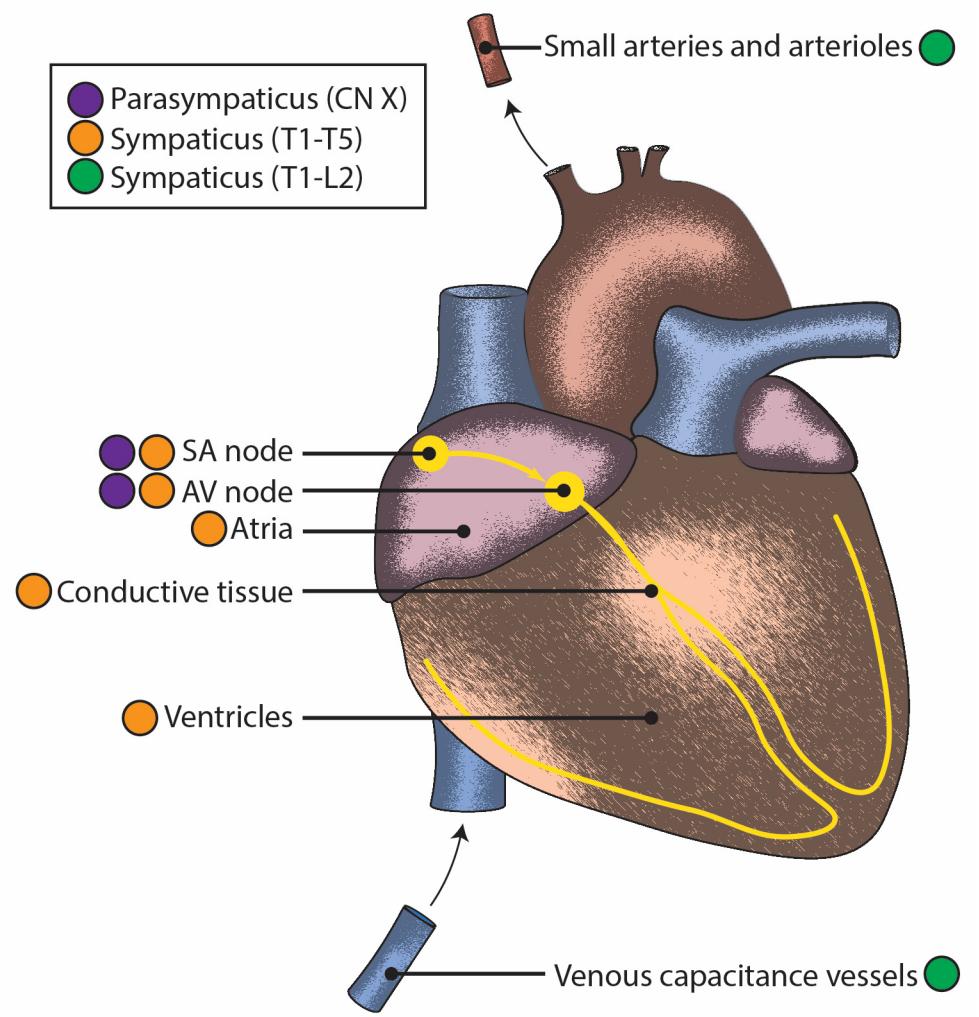


Figure 2. The autonomic innervation of the cardiovascular systems[44-46]
AV= atrioventricular; CN= cranial nerve; L= lumbar segments SA= sinoatrial; T= thoracic segments

Cardiovascular secondary health conditions

In Table 2, common cardiovascular SHCs in cervical and upper thoracic SCI are described. Cervical and upper thoracic SCI results in the loss of the supraspinal cardiovascular sympathetic control due to interrupted sympathetic transmission across the lesion site.[50] The reduced sympathetic activity to the cardiovascular system leads to lower heart rate and blood pressure.[50]

In addition, both hypotension and hypertension can occur in response to specific stimuli.[50] Orthostatic hypotension may occur, for example during transfers, as the constriction of venous capacitance vessels is impaired.[51] Transient episodes of hypertension due to noxious or non-noxious stimuli below the NLI is referred to as autonomic dysreflexia (AD).[50] AD may range from asymptomatic to, in rare cases, severe consequences causing life-threatening complications, including cardiac dysrhythmias, even with a fatal outcome.[50,52] The pathophysiology of AD is not fully understood but believed to be due to the loss of supraspinal control of SNS activity.[50] Numerous peripheral stimuli can trigger AD, such as bladder or bowel distension.[53] The peripheral stimuli will cause afferent activity to the spinal cord segments below the NLI, which activate sympathetic discharge causing vasoconstriction below the NLI.[54] The sympathetic activity below the NLI cannot be counteracted due to the loss of supraspinal control.[50] In response, vasodilatation occurs above the NLI (causing the symptoms above the NLI, such as headache and nasal congestion) and increased parasympathetic activity to the heart to reduce the cardiac output.[50]

The loss of supraspinal sympathetic control also results in blood pressure variability due to the continuous exposure to stimuli triggering orthostatic hypotension and AD.[55] In addition, the AD causes a vulnerability for cardiac dysrhythmias.[50]

Cardiovascular functional impairments are well-known in people with cervical and upper thoracic SCI. However, comprehensive assessments of the cardiovascular system in people with long-term SCI are scarce.

Table 2. Cardiovascular autonomic dysfunction in long-term cervical and upper thoracic SCI[50]

Secondary health condition	Definition
Bradycardia	Heart rate <60 beats per minute
Hypotension	Systolic BP <90 mmHg
Autonomic dysreflexia	An increase in systolic blood pressure >20 mmHg above baseline, the following symptoms may be present: headache, flushing, piloerection, nasal congestion, sweating above and vasoconstriction below the NLI, and dysrhythmias
Orthostatic hypotension	Drop in systolic BP≥20 or diastolic BP ≥10 mmHg at 3 min of body position change from supine to standing* or head-up tilt to at least 60°

BP= blood pressure; NLI= neurological level of injury
*Definition from the general population

Cardiovascular disease

Cardiovascular disease (CVD) includes several diseases and is one of the major causes of death in SCI.[20,21,56] CVD is predominantly caused by atherosclerosis, which, in turn, can cause acute myocardial infarction and stroke.[57] CVD include also

other diseases such as cardiac dysrhythmias, heart failure, hypertension, valvular heart diseases, pulmonary embolism and deep vein thrombosis.[58]

Groah et al (2001)[58] investigated CVD epidemiology in 545 people (mean age 57 years) with SCI and a minimum of 20 years after injury. In that study, CVD events and age-adjusted incidence rates were reported and demonstrated a relative CVD risk of 1.16 (95% confidence intervals (CI): 0.93-1.46) in people with tetraplegia (AIS A-C) as compared with people with paraplegia (AIS A-C). The contribution was largely due to dysrhythmias, valvular heart diseases and "other CVD" (including a broad spectrum of conditions such as congestive heart failure and venous insufficiency).[58] Corresponding relative risk for coronary heart disease and cerebrovascular disease in participants with tetraplegia compared to paraplegia were 0.30 (95% CI: 0.13-0.70) and 5.1 (95% CI: 1.2-21.2), respectively.[58]

CVD is attributable to a substantial proportion of the causes of death in SCI. In 2005, Garshick et al.[20] reported results from 37 deaths in a prospective assessment of SCI mortality in 361 men between 1994 and 2000. CVD was a factor in 40.5% of the deaths (primary 21.6% and secondary 18.9%).[20] Finally, beyond the exposure to cardiovascular dysfunction[50] that may contribute to the development of CVD,[59] several other CVD risk factors frequently occur among people with SCI. These include diabetes, obesity, dyslipidaemia, chronic kidney disease and physical inactivity.[60-64]

Despite increased attention to cardiovascular SHCs, many questions are still unanswered. To guide future research efforts and thereby improve the clinical management to increase life expectancy, we need an increased knowledge of cardiovascular dysfunction, CVD and CVD-related risk factors among people with SCI many years after injury.

Pulmonary physiology

The gas exchange between the environmental air and the blood is the major function of the pulmonary system.[65] In Figure 3, a schematic diagram of the process is presented.

Gas exchange

Gas exchange is due to ventilation (inspiration and expiration) and perfusion of the alveoli.[66] Inspiration is due to activation of respiratory muscles, whereas expiration, at rest, is due to passive forces.[67] Perfusion of the alveoli means the flow of deoxygenated blood from the body to alveolar capillaries.[66] Gas exchange is primarily due to diffusion between the aerated alveoli and the capillary blood.[66] Factors affecting the diffusion are the alveolar surface area and the diffusion distance from air to the blood.[66]

Lung compliance, chest wall compliance and airway resistance along with the ventilation rate are components facilitating ventilation. Lung compliance means the alveolar surface tension and the elastic properties of the surrounding tissues.[68] If the surface tension is increased, the alveoli will not be allowed to expand.[69] The elasticity is how easily the lung tissue return to its original configuration (similar to a rubber band).[70] The chest wall compliance is in balance with the lungs' elastic properties where the former tries to expand the lungs and the latter tries to decrease lung volumes.[71]

Airway resistance is primarily determined by the calibre of the airways.[72] Lung volume is another important determinant as lower lung volume causes decreased functional residual capacity (FRC), which results in a loss of elastic recoil acting to keep the airways open.[72,73] Airflow turbulence is another determinant of the airway resistance.[74] If the airways are constricted or collapsed due to lower lung volumes the flow will be more turbulent and cause an increase in airway resistance.[73,74]

Muscles of respiration

The mechanical properties of the pulmonary system determine the need of respiratory muscle force.[75] Primary inspiratory muscles are the diaphragm and external intercostal muscles.[76] Accessory inspiratory muscles can be recruited in case of increased ventilation demand.[77] In case of a forceful expiration (for example coughing), internal intercostal, subcostal, and abdominal muscles are recruited.[77]

Nervous control of ventilation and pulmonary vasculature

Ventilation is automatic and is originated and coordinated by the respiratory centre located in the brainstem.[78,79] Similarly, the pulmonary vasculature is controlled from the brain stem.[79] Sensory information is provided from peripheral and central chemoreceptors (arterial PO_2 levels) and mechanoreceptors (airways and pulmonary vasculature) in the pulmonary system.[79] The ventilation is adapted depending on the current demands, for example through the ventilation rate.[79]

The perfusion, on the contrary, is mainly controlled locally, without neural control, in response to alveolar PO_2 levels adapting the blood flow depending on the current demands.[80] However, autonomic activity in response to central arterial PO_2 levels constrict or dilatate the pulmonary vasculature to adapt the vasculature to the local changes in alveolar blood flow.[81]

The autonomic regulation of the airways and the pulmonary vasculature are analogous to the cardiac coordination; parasympathetic and sympathetic activity have opposing effects and is provided by the vagal nerve and the upper thoracic spinal segments.[79,82] Parasympathetic activity causes a decrease in airway calibre and vasodilatation, whereas sympathetic activity results in increased airway calibre (β-adrenergic receptors on airway smooth muscle but functional innervation has been suggested) and vasoconstriction.[81,83,84]

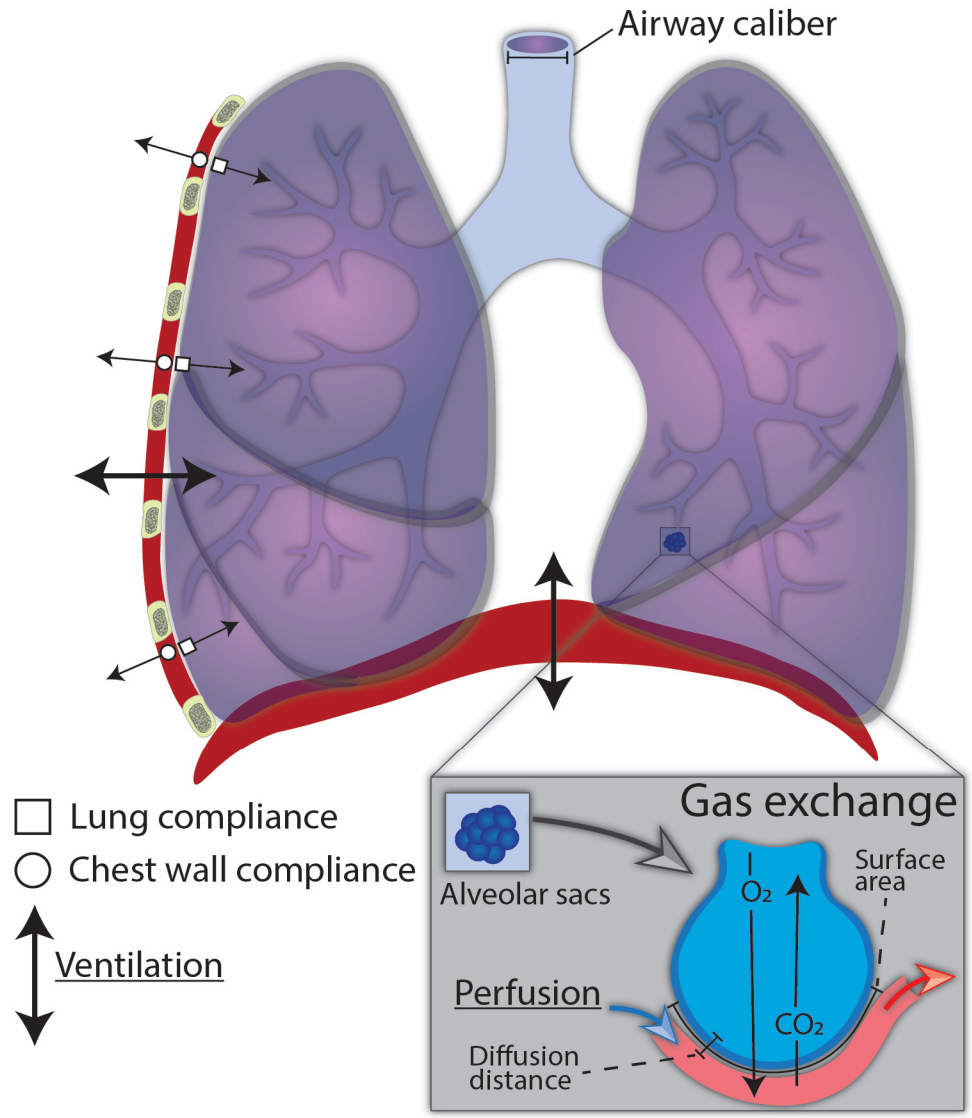


Figure 3. Pulmonary physiology[65-74]

The gas exchange in the alveoli is due to ventilation and perfusion. The actions of inspiratory respiratory muscles (red) expand the thoracic cage resulting in a lower pressure and the inflow of air. At rest the lung compliance (square) passively forces the lungs to return to their original configuration causing outflow of air. The lung compliance is in balance with the chest wall compliance (circle). Thus, the flow of air through the airways is due to the change in pressure. The flow is determined by the airway resistance. According to Poiseuille's Law: $Q = \pi Pr^4/8\eta l$ (Q=flow rate, P=pressure, r=radius, η= viscosity, l=length) the airway caliber is a significant determinant of the airway resistance.
In the ventilated alveoli the gas exchange between the air and the blood occurrs. Deoxygenated blood flows to capillaries surrounding the alveoli. The regulation of the perfusion is mainly local due to changes in alveolar PO_2 levels. The exchange of O_2 to the blood and CO_2 to the air occurrs by diffusion. Structural factors facilitating the diffusion are the diffusion distance from the air within the alveoli to the blood and the alveolar surface area.

Pulmonary secondary health conditions

In Figure 4, a schematic diagram of pulmonary SHCs in SCI are presented. SCI results in a neuromuscular pulmonary dysfunction due to a varying degree of paralysis of the muscles of respiration and depending on the NLI and AIS.[43] The neuromuscular pulmonary dysfunction limits the expansion of the lungs causing a restrictive pulmonary disease.[85] This is characterized by reduction of total lung capacity, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1).[86] A restrictive spirometry pattern in the general population has been associated with CVD, various risk factors for CVD and increased mortality.[87]

Due to the segmental organization of the spinal cord increased NLI will result in a more pronounced reduction in lung function, where the lower NLI (below T6) have FVC in the normal range (i.e., >80% predicted) and lumbar SCI about 100%.[43] In people with high-cervical NLI (C1-C4), ventilation may depend on the continuous use of a ventilator due to paralysis engaging the diaphragm.[88]

Accessory respiratory muscles innervated from segments above the NLI can compensate and improve ventilation.[89] The paralysis can also cause paradoxical breathing as the anteroposterior diameter decreases during inspiration because of the paralysed external intercostals and the increased abdominal compliance.[43]

One fundamental difference of the neuromuscular dysfunction in SCI compared with other neuromuscular conditions, for example amyotrophic lateral sclerosis, is that the expiratory function is compromised to a greater extent than the inspiratory function.[43] This is because the diaphragm, being the primary inspiratory muscle, is innervated from rostral segments and the primary expiratory muscles, the abdominal muscles, are innervated from caudal segments.[43] The reduced expiratory muscle strength causes weak cough.[43,89]

In addition to the neuromuscular impairments, the supraspinal pulmonary sympathetic control in cervical and upper thoracic SCI is compromised due to the interruption of sympathetic transmission across the lesion site.[82] Accordingly, data suggest a reduction in airway calibres due to increased cholinergic tone and increased airway resistance in people with tetraplegia.[84]

Furthermore, there are factors frequently occurring in cervical and upper thoracic SCI which indirectly affects pulmonary functions. Positioning has an effect due to the paralysed abdominal muscles.[88] In the seated position, the diaphragm is flattened due to that abdominal contents fall forward and impair diaphragm function.[88] Therefore the vital capacity is greater in the supine position.[88] Obesity and chest deformations following paralysis may further decrease the lung volumes thereby causing a more severe restrictive pulmonary disease.[86,90]

Pulmonary functional impairments are well-known in people with cervical and upper thoracic SCI. However, comprehensive assessments of the pulmonary system in SCI in people with long-term SCI are scarce.

Pulmonary functional impairments predispose people with SCI to respiratory complications, which ultimately is one of the major causes of death.[20,21] The reduced ability to expand the lungs and impaired cough may lead to atelectasis, stagnation of secretions, and pneumonia.[43]

There is a paucity of data of pulmonary infections in the chronic stage of SCI. A recent review identified five studies, however only two of these were reporting data more than five years after injury.[91] None of these two studies[92,93] reported pneumonia exclusively. One study[92] reported self-reported occurrence of "pulmonary complications" in the last year, whereas the other[93] reported atelectasis and pneumonia in combination. Nevertheless, these studies confirmed the relationship between age and pulmonary complications, in agreement with the general population, where the incidence of pneumonia is rapidly increasing in old age.[92-94]

Finally, the pulmonary dysfunction also predisposes people with SCI to sleep disordered breathing, especially in people with tetraplegia, where the prevalence of moderate sleep disordered breathing is about 60%.[95] The most common condition is obstructive sleep apnea, which is associated with CVD and increased mortality in the general population.[95,96]

Increased knowledge of pulmonary dysfunction and pulmonary complications among people with SCI many years after injury is therefore paramount to guide future research, to improve the clinical management and increase life expectancy.

In summary, cardiopulmonary functional impairments are well-known after SCI. Cardiopulmonary diseases in people with SCI reduce the life expectancy. Rostral NLI and completeness of injury are related to reduced life expectancy. Comprehensive assessments of the cardiopulmonary systems in people who have lived many years with their injury are lacking. Consequently, there is a need to 1) improve the knowledge of cardiopulmonary health in long-term SCI and 2) target people with higher NLI and greater injury severity, who are the most vulnerable.

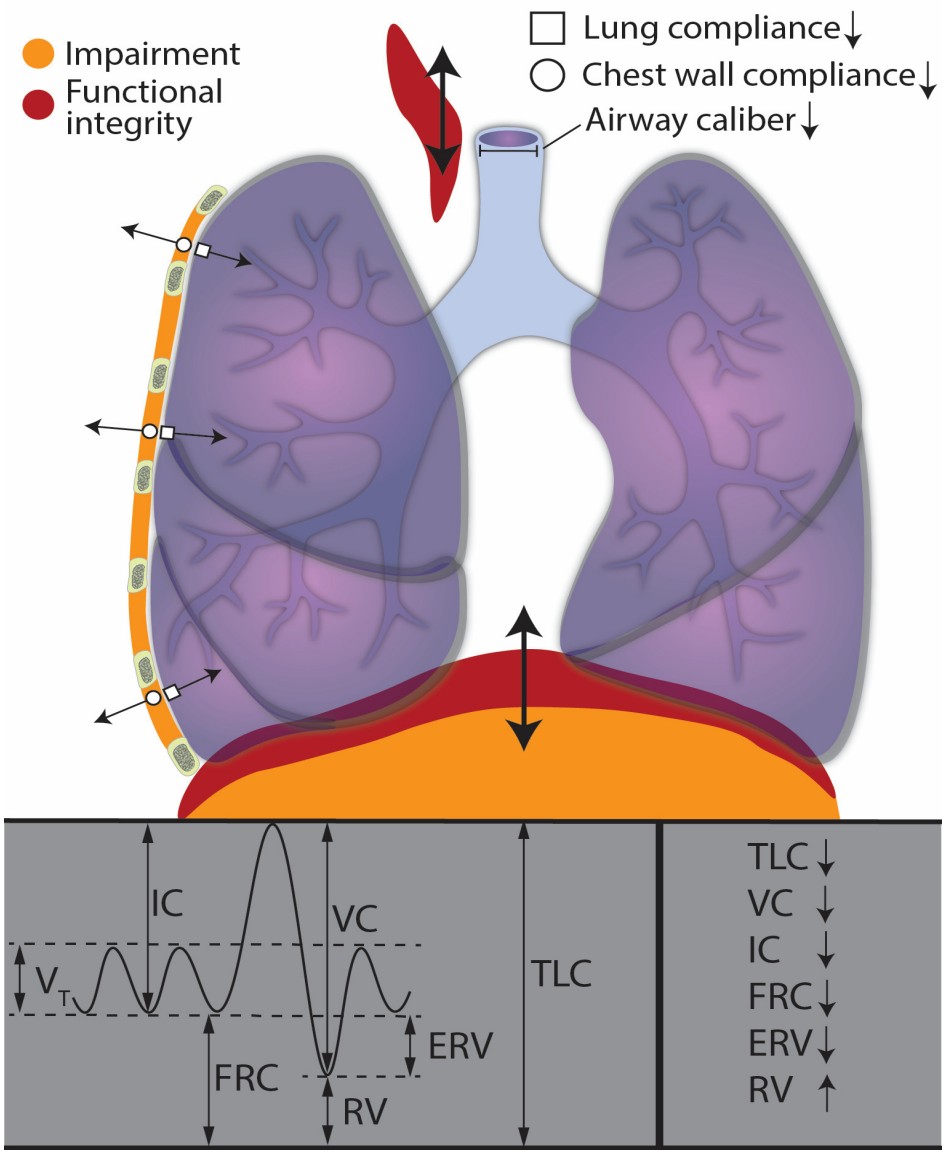


Figure 4. Schematic diagram of pulmonary dysfunction in cervical and upper thoracic SCI[43,84,88,89]

Neuromuscular impairment (orange) causes lower lung volumes and a restrictive pulmonary disease. NB functional integrity of the respiratory muscles is due to the neurological level of injury and thus the diaphragm can be impaired and functional integrity of the intercostal muscles preserved. Functional integrity of the diaphragm and accessory muscles (red) facilitates ventilation through vertical expansion of the thoracic cage and as the intercostal and abdominal muscles are impaired (orange) the anterioposterior diameter may at the same time decrease causing paradoxical breathing. Lung compliance and chest wall compliance decrease due to factors such as lower lung volumes and stiffening of the rib cage. Airway resistance increases probably due to lower lung volume and thereby lower FRC, in combination with a lower sympathetic tone.

ERV= expiratory reserve volume; FRC= functional residual capacity; IC= inspiratory capacity; RV= resiudal volume; TLC= total lung capacity; VC= vital capacity; V_T= tidal volume

Rationale

At the point of the initiation of this thesis project in 2017, there was a growing body of evidence of health hazards regarding cardiopulmonary diseases in the aging SCI population. Cardiopulmonary diseases are the two major causes of death in people with SCI and contribute to the decline in improvement of life expectancy.[18,20,21] At the same time there was a paucity of studies comprehensively assessing cardiopulmonary health and more specifically among people who have lived many years with their injury. Previous studies on cardiopulmonary health were fairly old and/or conducted on younger participants with shorter time since their injury.[1,20,55,58,84,97-137] In addition, studies were either not population-based or compared with controls.[1,20,55,58,84,97-115,117-137]

Altogether, this emphasized the need for a greater understanding of cardiopulmonary health in people with SCI many years after injury and specifically in people with cervical and upper thoracic SCI. This population is especially vulnerable as they have impairments directly affecting cardiopulmonary neurological modulation and have the lowest life expectancy.[18,29,43,50] A comparison with matched controls from the general population was also warranted to understand cardiopulmonary health specifically for people with cervical and upper thoracic SCI.

The increased knowledge generated from the studies in this thesis is expected to be used to formulate new hypotheses to direct future research efforts. Furthermore, a broad and in-depth description of cardiopulmonary health in a population-based sample generate insights which have implications for the clinical management. Thereby, this thesis provides one piece to bridge the knowledge gap towards the future development of SCI standards of care aiming to contribute to increased longevity in people with SCI.

Aims

The overarching aim of this thesis was to describe and explore cardiopulmonary health in middle-aged people with long-term cervical and upper thoracic SCI in the Skåne region, Sweden, and to compare the results with matched controls from the general population.

Specific aims

In a cohort of middle-aged people with cervical and upper thoracic SCI, AIS grades A-C and at least 5 years after SCI:

- describe the demographic characteristics;
- describe anthropometrics, cardiopulmonary lifestyle factors, comorbidities, cardiopulmonary symptoms (including cardiovascular SHCs), and current medications;
- describe CVD risk factors, and compare findings with controls;
- describe cardiovascular autonomic functions and determine whether findings are different as compared with controls;
- describe coronary and carotid atherosclerosis, and compare findings with controls;
- describe functional and structural impairments of the pulmonary system and determine if findings differ from controls;
- determine if NLI is related to cardiovascular autonomic functions, and functional and structural impairments of the pulmonary system;
- determine if age among the participants and controls is related to structural impairments of the pulmonary system

Methods

To increase our knowledge of cardiopulmonary health in people with cervical and upper thoracic SCI many years after injury I designed, in collaboration with my supervisors, the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment (SPICA). SPICA is a population-based descriptive and exploratory cross-sectional study of middle-aged people with long-term traumatic cervical and upper thoracic SCI.

This thesis is based on subsets of the data collected in SPICA. Therefore, this section begins with a brief background to describe SPICA, including an overview of the recruitment procedure and data collection. Thereafter, the data collection and the statistical analyses in the four studies included in this thesis are summarized.

The data collection of SPICA was based on the baseline protocol of the Swedish CArdioPulmonary bioImage Study (SCAPIS)[3] in combination with study specific assessments. Matched control data collected in SCAPIS are used to compare people with SCI with the general population. The studies comprising this thesis conform to the guidelines of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology).[138]

Design of the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment

Setting and recruitment

The participants in SPICA were community-dwelling and recruited through databases (comprising about 700 people with SCI in southern Sweden, including the Skåne region) at the SCI Unit, Skåne University Hospital. The SCI unit serves the catchment area of the Skåne region, Sweden (1.3 million people in 2018) and provides primary rehabilitation and lifelong follow-up for people with SCI in the Skåne region, Sweden.

In Figure 5, a flow chart of the recruitment process is presented.

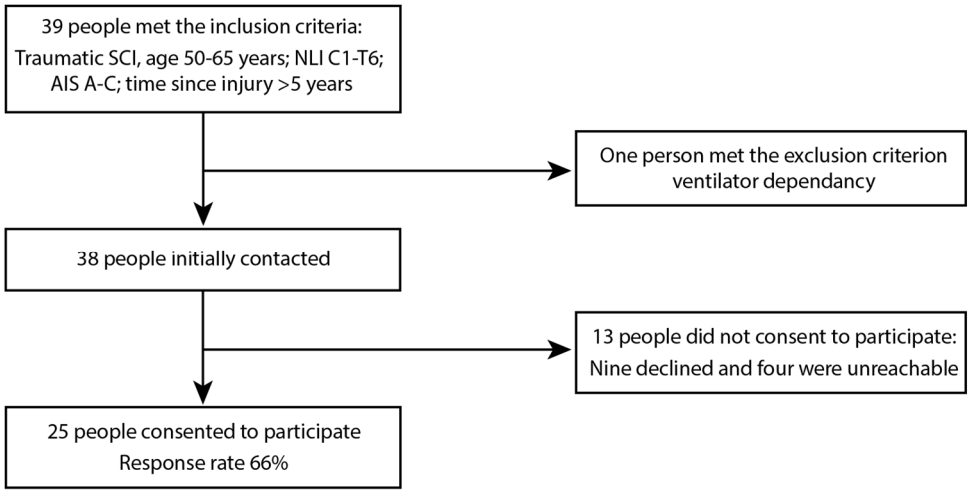


Figure 5. Recruitment flow chart of the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment (SPICA)
AIS= American Spinal Injury Association impairment scale; NLI= neurological level of injury

The reason for exclusion of NLI below T6 and AIS D was to create a uniform study population of participants with severe neurological cardiopulmonary impairments and the lowest life expectancy.

Data collection procedure

In Figure 6 and Table 3, the data collection in SPICA is presented.

Data were primarily collected during three separate study visits at the SCAPIS study site at the Skåne University Hospital in Malmö, Sweden from January to May 2018. In addition, reviews of medical records from the last five years were performed, and a study-specific questionnaire (Appendix) and self-reported assessments tools were administered at the first study visit.

I actively participated in all the data collection and performed the parts of the data collection which were not included in the SCAPIS baseline protocol (except for the ISNCSCI and Modified Ashworth scale in one participant which were performed by Lena Wapner, registered physiotherapist at the SCI unit).

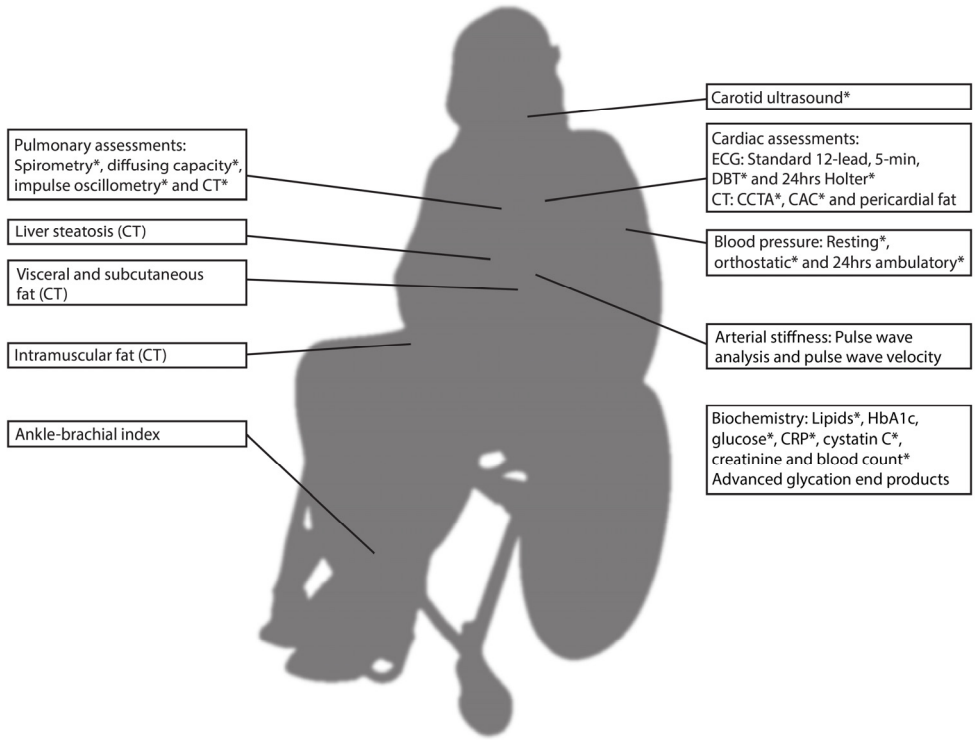


Figure 6. Overview of the functional and structural assessments of the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment (SPICA)

*Indicating assessments used to collect data for the four studies of this thesis

CAC= coronary artery calcium; CCTA= coronary computed tomography angiography; CRP= C-reactive protein; CT= computed tomography; DBT= deep breathing test; ECG= electrocardiogram; HbA1c= glycosylated hemoglobin

Overview of this thesis

The first study comprising this thesis describes the design and cohort characteristics of SPICA. Then, the three subsequent studies describe cardiopulmonary function and structure of the cohort and compare the results with matched controls from the general population. In Table 4, an overview of the four studies included in this thesis are presented.

Table 3. Additional study-specific data collected in the Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment (SPICA)

Data collection	Procedures and variables
Accelerometry	Ambulatory activity registration for one week using an accelerometer
Anthropometry*	Body weight, body height, waist and hip circumference
Autonomic dysfunction following spinal cord injury (ADFSCI)*[1]	Self-reported ratings of presence and severity of cardiovascular autonomic dysfunction in SCI
Hospital anxiety and depression scale (HADS)[139]	Self-reported ratings of symptoms of anxiety and depression among physically ill persons
International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI)*[2]	Clinical examination assessing the neurological level of injury and the extent of injury according to the American Spinal Injury Association injury scale
Medical records review and interview*	Gender, age, age at injury, injury etiology, medical history and prescribed medications
Modified Ashworth scale (MAS)[140]	Clinical examination measuring spasticity in the upper and lower extremities
Sense of Coherence (SOC)[141]	Self-reported ratings of the 3 dimensions of the SOC concept: comprehensibility, manageability and meaningfulness
Spinal cord independence measure, third version (SCIM III)*[142]	The third version of SCIM III is a disability scale for clinicians assessing activity limitations after SCI comprising three subscales: self-care, respiratory and sphincter management, and mobility
Spinal cord injury spasticity evaluation tool (SCI-SET)*[143]	Self-reported ratings of the the impact of spasticity on activities of daily living, considering both useful and interfering effects
Study-specific questionnaire*	Life satisfaction, lifestyle, medical history, current medications, pain, cardiopumonary symptoms and living conditions

*Indicating data or subset of data used in the four studies of this thesis
SCI= spinal cord injury; SCIM= Spinal Cord Independence Measure; SOC= Sense of Coherence

Table 4. Overview of the four studies in the thesis

	Study I	Study II	Study III	Study IV
	SPICA	**Cardiopulmonary Function and Structure**		
Aim	To present an overview of the methodology of the SPICA, compare the demographics of the participants and nonparticipants, to describe the demographic characteristics of the participants, and describe anthropometrics and cardiopulmonary lifestyle factors, comorbidities, cardiopulmonary symptoms, current medications, and secondary health conditions of the participants	To describe cardiovascular autonomic functions and determine whether findings are different as compared with matched controls from the general population, and explore if NLI is related to cardiovascular autonomic functions	To describe coronary and carotid atherosclerosis, and CVD risk factors and compare findings with matched controls from the general population	To describe functional and structural impairments of the pulmonary system and determine if findings differ from matched controls from the general population. To determine if NLI is related to the functional and structural impairments, and determine if age among the participants and controls is related to the structural impairments
Design	Study protocol and cross-sectional study	Cross-sectional studies with matched controls		
Participants	25 middle-aged people with cervical and upper thoracic spinal cord injuries, AIS grades A-C and injury duration more than 5 years			
Controls		125 matched controls from the general population		100 matched controls from the general population
Data collection	Study-specific questionnaire, anthropometry, medical records review, ADFSCI, SCI-SET, SCIM III, biochemistry and SCORE	DBT, 24 hrs ambulatory ECG and BP, and orthostatic test	CCTA, CAC, carotid ultrasound and CVD risk factors	Spirometry, diffusing capacity, IOS and CT
Analyses	Mann-Whitney U test and the Fisher's exact test	Conditional logistic regression		
		Paired samples t test and Spearman rank correlation	Mann-Whitney U test	Sensitivity analyses, Spearman rank correlation, logistic regression and interaction analysis

ADFSCI= Autonomic Dysfunction Following Spinal Cord Injury; AIS= American Spinal Injury Association Impairment Scale; BP= blood pressure; CACS= coronary artery calcium; CCTA= coronary computed tomography angiography; CT= computed tomography; CVD= cardiovascular disease; DBT= deep breathing test; ECG= electrocardiogram; IOS= impulse oscillometry; NLI= neurological level of injury; SCIM III= Spinal Cord Independence Measure; SCI-SET= Spinal Cord Injury Spasticity Evaluation Tool; SCORE= Systematic Coronary Risk Evaluation; SPICA= Swedish SPinal Cord Injury Study on Cardiopulmonary and Autonomic Impairment

Data and assessments

There are several different assessments used to collect data in this thesis. For more detailed methodological descriptions, see Appendices.

Sociodemographics and injury characteristics

Data on gender and age were obtained from the participants' medical records. Marital status, vocational situation and educational level were obtained from the study-specific questionnaire.

Injury aetiology and age at injury were collected from the medical records and confirmed during the interview; time since injury was thereafter calculated. NLI and AIS were obtained from the participants' medical records and confirmed during the clinical examinations (i.e., a complete ISNCSCI examination was rarely necessary).

Anthropometrics and lifestyle factors

Body weight was obtained using a portable scale for wheelchairs. Body height and waist circumference (WC) were measured in a supine position using a flexible measuring tape. Body mass index (BMI) was calculated from the height and weight measures.

Data on lifestyle-related factors (smoking and physical activity) were obtained from the study-specific questionnaire.

Medical history

Data on medical history (comorbidities, cardiopulmonary symptoms, current medications, and secondary health conditions) were obtained from the five-year medical record review of hospital medical records, the study-specific questionnaire (see Appendix) and the Autonomic Dysfunction Following Spinal Cord Injury (ADFSCI).[1] Thus, comorbidities (based on SCAPIS study-specific questionnaire) and current medications were obtained from the questionnaire. These could be complemented and validated through the medical record review and, in case of ambiguities, confirmed through the interview. Occurrence of pneumonia and recurrent deep vein thrombosis data were obtained from the medical records.

Chronic kidney disease data were obtained from absolute glomerular filtration rate calculations using obtained cystatin C^{144} and anthropometry data.

CVD risk data according to the Systematic Coronary Risk Evaluation (SCORE) were calculated from obtained data on gender, age, systolic blood pressure, total cholesterol, and smoking status using the Swedish SCORE chart.[145,146]

Before including the ADFSCI in the study protocol, a forward-backward translation was performed after approval from the developer Dr Andrei Krassioukov.

Biochemistry

Total cholesterol, non-high-density lipoprotein (HDL) cholesterol, plasma glucose, cystatin C, hemoglobin and high-sensitivity C-reactive protein (CRP) were determined from venous blood samples at the Department of Clinical Chemistry, Skåne University Hospital in Malmö, Sweden. Blood samples were collected after an overnight fast.

Cardiovascular functional and structural assessments

Eight different assessments were used to collect data on cardiovascular functions and structures (see Definitions for descriptions of cardiovascular variables).

Electrocardiogram

Heart rate variability (HRV) was assessed using the deep breathing test (DBT) and 24 hrs Holter electrocardiogram (ECG) analyses.

DBT was performed according to the SCAPIS protocol.[147] After a 5-minute rest and while the participants were taking deep breaths for one minute a 12-lead ECG (precordial leads placed on the chest and the extremity leads placed centrally) was recorded in the supine position. The participants were instructed to breathe through the nose if possible and inhale and exhale each time over a period of 5 seconds. Measurements of the mean and median expiration–inspiration difference (E-I), expiration–inspiration ratio (E/I), standard deviation of heart rate (SD_{HR}), mean circular resultant (MCR) and root mean square of successive differences (RMSSD) were performed. These variables are considered important indicators for parasympathetic cardiovagal function where $E\text{-}I_{median}$, E/I and MCR being the most resistant to anomalies such as premature ventricular contractions.[10]

24 hrs Holter ECG signal analysis was recorded and analysed (cf. Figure 7). Measurements of standard deviation of the normal-to-normal interval (SDNN), RMSSD, low frequency (LF), high frequency (HF) and LF/HF ratios were performed as these correspond to different cardiovascular autonomic functions (see Definitions).[12] Atrial fibrillation was present in one participant during the 24 hrs registration. These data were excluded due to the substantial distortion of the HRV assessment.

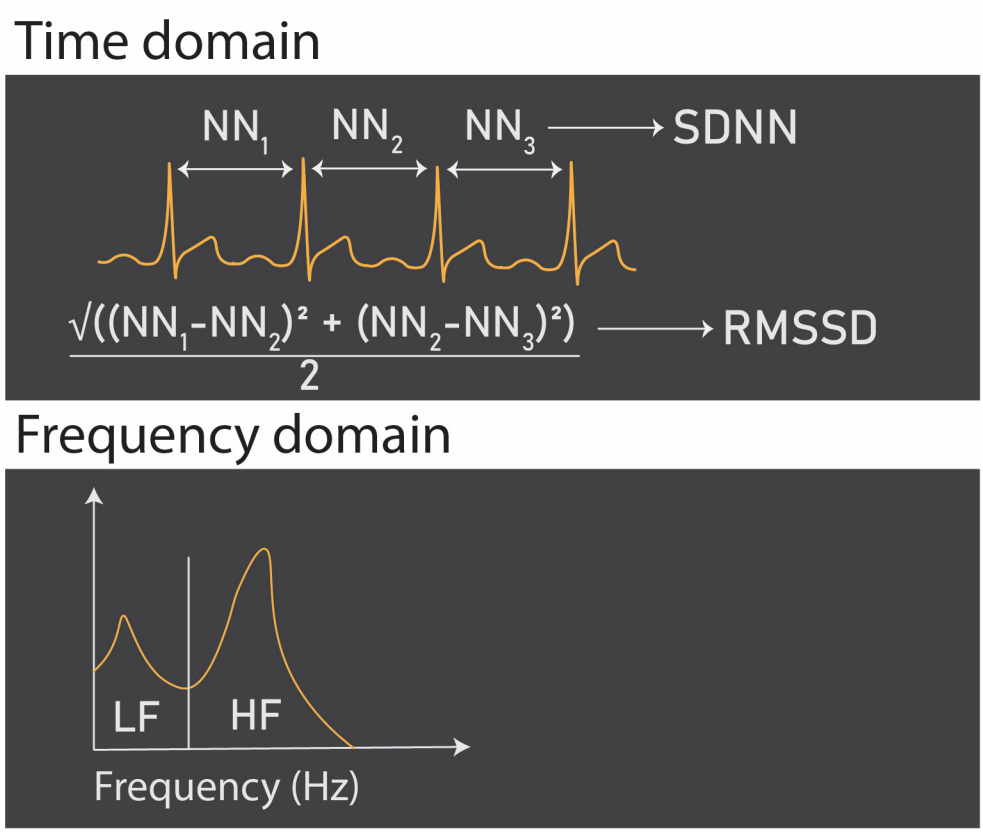


Figure 7. Heart rate variability variables[12]

Time domain variables are based on the HRV changes over time. The schematic recording includes only three NNs, thus for the RMSSD there are only two successive differences. Frequency domain variables show how much power (ms^2) lies within each frequency band (schematically depicted the LF and HF). The power is the area under the curve. From LF and HF measurements the LF/HF ratio is calculated. HF=high frecuency; LF= low frequency; NN; normal-to-normal interval; RMSSD= root mean square of successive differences; SDNN= standard deviation of the normal-to-normal interval

Blood pressure

Resting systolic and diastolic blood pressure measurements were made twice after a 5-minute rest and bilaterally using an automatic device.

Orthostatic blood pressure was obtained from the calculated difference in mean blood pressure from the supine and the seated position. First, after a 5-minute rest two measurements were performed with one minute between the measurements in a supine position. Thereafter the participants were assisted or raised up to a seated position and instructed to not talk for three minutes and remain absolutely still. In the control group, a rise to a standing position was instructed. Two blood pressure measurements were performed after three minutes without any pause between these measurements.

Ambulatory 24 hrs blood pressure (ABPM), blood pressure variability and circadian blood pressure patterns were assessed from measurements of blood pressure every 30 minutes. In one participant, there were few valid measurements, and the data were therefore excluded.

Computed tomography

Computed tomography (CT) was used to assess coronary atherosclerotic plaques and coronary artery calcium (see Definitions) according to the SCAPIS study protocol.[148]

The presence of plaques was determined according to the modified American Heart Association classification using coronary CT angiography (CCTA), with contrast media injection and electrocardiogram-gated imaging.[148] Four participants had contraindications for the administration of contrast media (allergy, kidney failure and not understanding Swedish) and were excluded.

Imaging of coronary artery calcium to measure coronary artery calcium score was obtained. The measurements were performed according to international standards.[6]

Two experienced radiologists individually analysed the CT images to avoid inter-rater bias. In four participants, issues with venous access caused missing CCTA data. One participant declined to perform the CT assessments and therefore CCTA and coronary artery calcium data were missing. Coronary artery calcium data were missing in one additional participant due to cardiac stenting.

Carotid ultrasound

B-mode ultrasonography imaging was used to determine the presence and sizes of atherosclerotic plaques in the common carotid artery, the bulb and in the internal carotid artery, and to measure the intima media thickness (IMT) in the bulb and the common carotid artery (see Definitions) according to international standards.[13,149] Two experienced biomedical scientists individually performed the analyses to avoid inter-rater bias. Ultrasound could not be performed in two participants due to technical matters. In one participant, anatomical difficulties caused an incomplete data collection.

In summary, to assess cardiovascular body functions ECG and blood pressure were performed in different physiological situations, for example during deep breathing and change in body position. From these measures calculations of different parameters corresponding to cardiovascular body functions were performed and further analysed. Assessment of the cardiovascular body structures were performed using advanced imaging to reveal the presence of atherosclerosis in both the coronary and carotid arteries.

Pulmonary functional and structural assessments

Four different assessments were used to collect data on pulmonary functions (described in Figure 8) and structures (see Definitions for descriptions of pulmonary variables).

Spirometry

Dynamic spirometry assessing lung volumes and flows was performed with the participants seated upright in their wheelchair according to international standards, adjusted for SCI.[150,151]

Slow vital capacity, FVC, FEV_1, FEV_1/FVC and maximal expiratory flow at 50% (MEF_{50}) measurements were performed. The predicted percent of vital capacity, FEV_1 and MEF_{50} were calculated from these measurements according to established methods.[11] The largest volume of slow vital capacity or FVC determined the vital capacity.

Diffusing capacity

The single breath method was used to measure diffusing capacity according to international standards.[9] The following variables were measured: diffusing capacity of the lungs for carbon monoxide (D_{LCO}), alveolar volume (V_A) and the carbon monoxide transfer coefficient (k_{CO}). The predicted percent, corrected for hemoglobin levels, of D_{LCO} and k_{CO} were calculated from these measures.[152]

Impulse oscillometry

Impulse oscillometry (IOS) was performed to assess respiratory impedance and thereby the mechanical properties of the pulmonary system.[4] The following variables were calculated: R5, R20, R5-R20, X5, AX and resonant frequency (Fres).

According to the SCAPIS protocol, the controls performed the pulmonary function tests 15 min after the inhalation of 400 µg salbutamol. The aim was to study chronic obstructive pulmonary disease (COPD) and identify people with COPD from people with asthma. For logistic reasons and the aim of SPICA, the participants in SPICA were not administered Salbutamol.

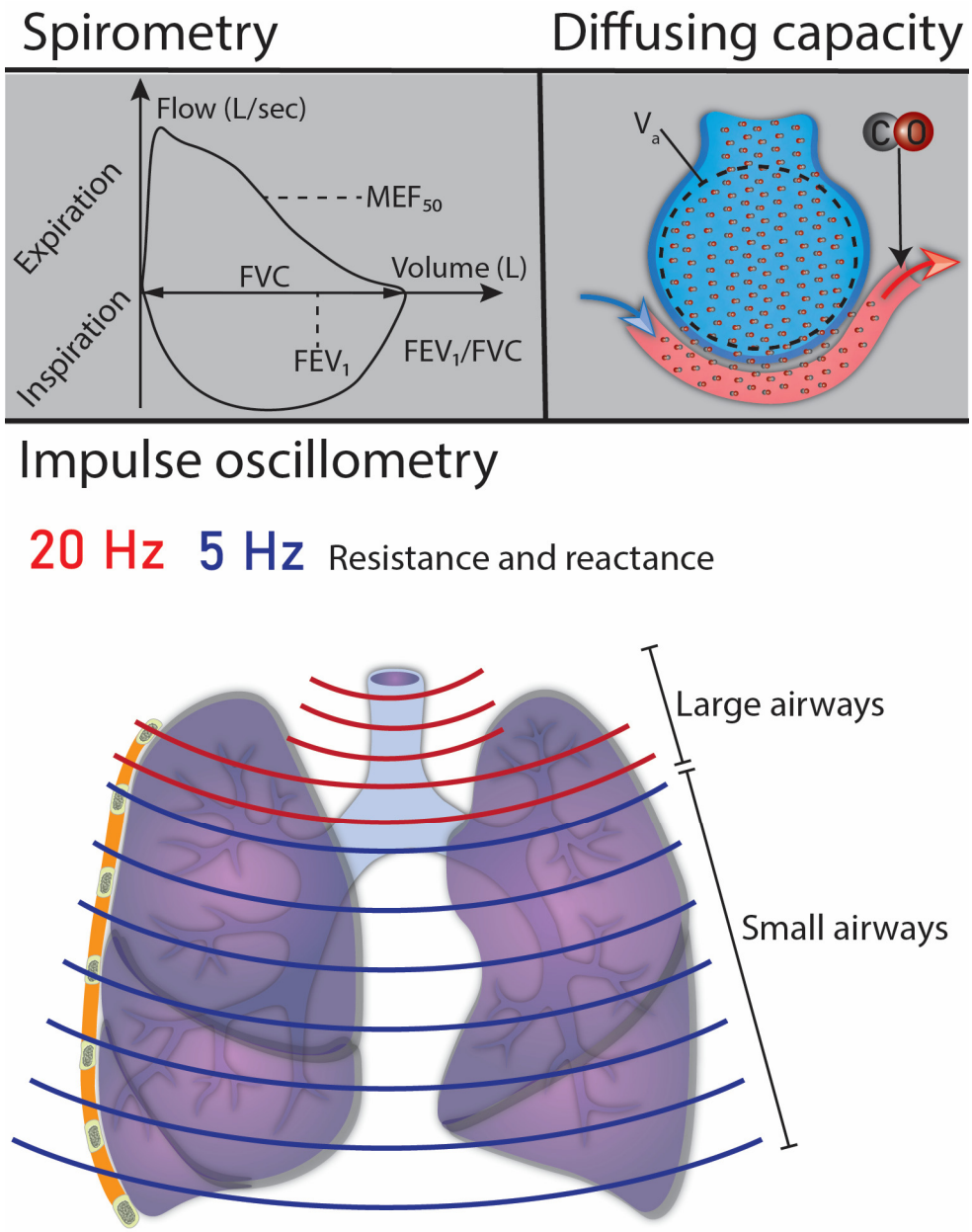


Figure 8. Pulmonary functional assessments[4,9,11]

Forced spirometry assesses volumes and flows. Diffusing capacity assesses the transfer of CO from inhaled air to the blood and the alveolar volume. Impulse oscillometry assesses the components resistance and reactance of the respiratory impedance. Sound waves are inhaled and travel through the airways. Lower frequencies travel further in the airways and therefore 5 Hz represents the total respiratory resistance, whereas 20 Hz represents large airways.

FEV_1= forced expiratory volume in 1 second; FVC= forced vital capacity; MEF_{50}= maximal expiratory flow at 50 % of the FVC; V_a= alveolar volume

Computed tomography

Imaging of pulmonary structural impairments were performed using high resolution CT scans of the full lung volume during inspiration and expiration. One experienced thoracic radiologist examined the images to avoid inter-rater bias and determined the presence of structural impairments according to international standards.[5]

In summary, to assess pulmonary body functions spirometry, diffusing capacity and IOS were performed. These assessments provide comprehensive data on ventilatory capacity, gas exchange and the mechanical properties of the pulmonary system. Additionally, CT was performed to determine the presence of structural impairments in the lungs.

Matched control data

In Study II-IV, matched control data were used from the 6 251 participants enrolled at the Malmö study site of SCAPIS from 2014 to 2018. Data were obtained after applications to the SCAPIS Data Mart (https://scapisdata.wlab.gu.se/Project/Index). Access to data and matching procedures were performed by SCAPIS.

There were three different sets of matched control data due to the different aims of the three studies. Matched control data were available from all the 6 251 SCAPIS participants. Therefore, there were several potential controls to one participant, which improve the statistical power.[153] In the first application (Study IV), control data at a ratio of 4:1 was obtained. The results in that study were in some instances close to statistical significance. In order to attain an even greater statistical power, the second application (Study II and III) was agreed at a ratio of 5:1 after discussions with collaborators in SCAPIS. More than five controls do not improve the power meaningfully.[153]

The control data from SCAPIS were collected both by the same staff as in SPICA and during the same time period. If there were more available controls than the ratio, the controls were chosen randomly. There were more matching criteria in Study IV as those criteria are important determinants of pulmonary function.

The matching criteria of Study II-IV are presented in Table 5.

The data collection of SCAPIS was not always complete for every individual and some of the assessments used in SPICA were optional at the SCAPIS study site in

Malmö. Thus, the obtained control data were not complete. There were, in general, at least four controls to every participant except for the DBT measures.

Table 5. Matching criteria of Study II-IV

Matching criterion	Study II	Study III	Study IV
Gender	X	X	X
Age	±2 year	±2 year	±1 year
Heigth[1]			±5 cm
Smoking status			Current (Yes/No)
Time period	12 months	12 months	6 months
CT imaging analysist[2]		2	1
Performed 24 hrs ambulatory assessments	Yes		
Performed cardiac CT assessments		Yes	

CT= computed tomography
[1]Weight or BMI were not matching criteria as these are not considered valid in people with SCI due to the changes in body composition after injury
[2]Few imaging analysists to avoid inter-rater bias

Data management and statistical analyses

Data were presented by means of descriptive statistics in all studies (mean, standard deviation, median, minimum, and maximum, and frequencies), and were assessed for normality.

Dropout analyses (Study I) were computed using the Mann-Whitney U test or the Fisher's exact test where appropriate.

Comparisons between participants with SCI and the matched controls (Study II-IV) were performed using conditional logistic regression, taking the matching into account. From these analyses p-values, odds ratios (OR) and 95% CI were calculated. In continuous variables, the OR and 95% CI indicate the odds of being a participant for a one-unit increase in the variable. In some variables, the presentation of the OR and 95% CI was not meaningful, as the variables were measured in very low or high values. This caused very wide or narrow 95% CIs and therefore they were not presented.

Highly skewed variables either were transformed or analysed using non-parametric statistics (Mann-Whitney U test). If data were missing among the participants, the corresponding control data were excluded.

The paired samples t test was used (Study II) to compare 24 hrs ambulatory measurements (day and night).

Spearman's rank correlation coefficient was used (Study II and Study IV) to assess correlations between NLI and cardiopulmonary variables.

In Study IV, sensitivity analyses of the conditional logistic regression analyses were computed for missing pulmonary function data among the controls using single imputation.

In Study IV, logistic regression was used to investigate associations between chronological age and pulmonary structural impairments (linear scars of atelectasis and any structural impairment). The ORs were calculated for the participants and controls, respectively. Then, age as an interaction variable (age multiplied with the presence of the structural finding) was used in conditional logistic regression analyses to determine whether the participants and controls ORs differed.

The statistical significance level was 95% (p-value <0.05 and CI confidence level of 95%); i.e., the null hypothesis is rejected if the probability of a Type I error is <5%. No corrections of the significance level, such as the Bonferroni, were performed to counteract the increased risk for Type 1 errors due to multiple comparisons. This was because of the low power and the exploratory design of SPICA. Also, due to the exploratory study design, no power calculation was performed in SPICA.

All statistical analyses were performed using the IBM SPSS Statistics Software (v 25, v 28 and v 29).

Ethical considerations

Throughout this thesis, there have been several ethical issues to reflect upon. The generation of new knowledge cannot be at the expense of the individual study participants interests and rights. Thus, international ethical principles for medical research have been developed.

In SPICA, the Declaration of Helsinki for research on humans has been followed.[154] Furthermore, ethical review is required by law in Sweden, according to the Ethical Review Act (2003:460), for research involving humans;[155] SPICA was approved by the Regional Ethical Review Board in Lund, Sweden (No. 2017/756).

The United Nations Convention on the Rights of Persons with Disabilities (CRPD) is another international legally binding instrument to set the minimum standards for rights of people with disabilities including health (article 25).[156] This means the rights of people with disabilities to enjoy the highest attainable standards of health. In that sense SPICA conforms to the intentions of CRPD as knowledge of cardiopulmonary health, specifically in people with long-term SCI, is largely unknown, impeding the potential to enjoy the highest standards of health in this population.

During the course of the study several specific ethical issues arose. The ethical review requires an informed consent. Thus, all participants received an invitation letter with written information about the study and contact details. Not every potential participant replied and therefore at least three attempts (phone calls) were made to contact them, and if people were still unreachable, a follow-up letter was sent to encourage contact.

This was the first clear ethical issue – my sincere wishes to enrol as many participants as possible because the targeted population is very small, meaning that each participant has a significant impact on the power of the study versus the doubts of the potential participant. I had to balance the information of potential benefits and not be too persuasive. Another ethical aspect was that I had a clinical relationship as a physician at the SCI unit with a few of the participants, which may have affected their decision to participate. I think that I managed this somewhat delicate task, even though it became clear to me that other people from the SCI unit encouraged participation.

The next ethical issue concerned the decision making of the participants. It is stated that during the first study visit the participants in SPICA received oral information about the study and about their rights to withdraw at any time (one participant used the right to withdraw after the second study visit). Thereafter the participants signed a written informed consent form. This is true, but the consent was, seemingly, not based on the information, as very few were interested in the details of the study. Participation was rather based on their *trust*. Trust, based on the institution: the SCI

unit and prior participation in SCI research conducted by our research group. The value of the informed consent – one of the fundamental principles of the ethical statements – was challenged. For whom was it? Nevertheless, in my opinion, if people place their trust in you, it carries an even greater responsibility to do the right thing and make the right decision.

The data collection procedures could potentially cause discomfort and travelling can pose a risk for pressure injuries in this population. Therefore, a person with SCI and a registered physiotherapist visited the study site before the data collection to ensure that the facilities were accessible. Specific pillows were bought to improve positioning when performing the CT assessments. Certificates for safe transportation to and from the study site were provided, if needed, to reduce the risk for pressure injuries. Radiation for imaging was kept as low as possible and potential risks for administration of contrast media injection were identified (four participants were therefore excluded). Overall, there were no complaints regarding the data collection procedures from the participants.

The participants came to the study site on three separate occasions, and I participated in all of the data collection procedures. Every participant was given the opportunity to return the ambulatory equipment (accelerometer and 24 hrs ECG and blood pressure) with the help from me, which meant that I visited some of the participants in their homes. Altogether, this caused an unforeseen close interaction with the participants, which I valued highly. This also gave me the opportunity to continuously give oral information about individual study findings and respond to any specific question. Trust was building and culminating when a study participant, who for a long time have had health issues, took the opportunity to express the wishes regarding cardiopulmonary resuscitation strategies to be registered in the medical records. An obvious relief for that person and an expression, which there never had been the space or context for during numerous previous contacts with health care.

During this close interaction, another ethical issue arose. Some participants expressed a belief that research in SCI in general had the objective to improve the neurological deficits after SCI; “maybe this will help me to improve”, when in fact, the objective was never to improve the neurological deficits after SCI. This was a challenge to address, due to the feelings that rose in me when acknowledging this hope among these participants, deficits that I could not affect. I tried to validate their feelings and still be quite frank about the objective of the study.

This notion reflected back upon my experiences of the “neglected” informed consent. People always have the liberty to reject participation for any reason. However, what about the opposite, when the participants are not necessarily interested in fully understanding the study’s purpose, despite the given opportunity, and participation is based on other reasons than an *informed* consent?

When the data collection and initial analyses were completed, all participants received a written summary of their study findings and shortly thereafter a follow-up phone call. Pathological findings were addressed during the study with no hesitation to establish further investigations or treatment.

Herein lies another ethical issue – the discrepancy between full autonomy and the potential to inflict harm in cases when there is no further treatment or specific management. I am myself much leaning towards autonomy, acknowledging people to both have the right to know and to have the competence to receive information concerning their health. However, among the participants pulmonary health issues, for example, were not expressed as the major concern I recognize from my own clinical perspective, and in part the rationale for the study. There are no additional guidelines on pulmonary management in this population to prevent pulmonary complications. Thus, I had to carefully balance the extent of information and the potential implications for the individual participant.

Results

In this section, the cohort characteristics are initially reported, thereafter the descriptive results and comparisons with controls regarding the cardiopulmonary variables, and finally associations between NLI and cardiopulmonary variables, and between pulmonary structural impairments and age. In addition, brief interpretations of the cardiopulmonary results are provided.

Cohort characteristics of SPICA

Sociodemographics and injury characteristics

In Table 6, the sociodemographics and injury characteristics of the participants in SPICA are presented. There were no significant differences regarding gender, age, or the injury characteristics between the 25 participants and 13 non-participants.

Anthropometrics and lifestyle factors

In Table 7, the anthropometrics and lifestyle factors of the participants in SPICA are presented. Most of the participants were classified as overweight or obese both according to the World Health Organization and the suggested SCI-adjusted cut-off values.[157] Four (16%) participants were engaged in regular leisure time physical activity.

Medical history

In Figure 9, the medical history of the participants in SPICA are presented. Cardiopulmonary comorbidities were present in some of the participants, obstructive sleep apnea being the most common comorbidity (n=7; 28%). In total, 18 participants (72%) were identified as having a high risk for CVD. Cardiopulmonary symptoms were rarely reported but self-reported SHCs affecting the cardiovascular systems were frequently occurring (AD n=17; 68%, and hypotension n=19; 76%, respectively). Almost all participants (n=23) were prescribed medications and baclofen was the most common (n=11) (for detailed descriptions of medications see Appendix).

Table 6. Sociodemographics and injury characteristics of the participants in SPICA

	n (%); Mean ± SD; Median, Min–Max
Sociodemographics	
Gender	
Women	5 (20)
Men	20 (80)
Age	58 ± 5; 58, 50-65
Marital status[1]	18 (72)
Vocational situation[2]	10 (40)
Educational level	
Low (elementary school)	1 (4)
Medium (upper secondary school, vocational training)	14 (56)
High (university or college degree)	10 (40)
Injury characteristics	
Age at injury	30 ± 12; 28, 7-56
Time since injury	28 ± 13; 31, 6-53
Neurological level of injury	
C1-C4	10 (40)
C5-C8	6 (24)
T1-T8	9 (36)
ASIA Impairment scale	
AIS A	15 (60)
AIS B	8 (32)
AIS C	2 (8)

AIS= ASIA Impairment Scale; ASIA= American Spinal Injury Association
[1]I.e., living in a relationship (married/cohabiting/partner)
[2]I.e., working full-time or part-time

Table 7. Anthropometrics and lifestyle factors of the participants in SPICA

	n (%)	Mean ± SD	Median	Min–Max
Anthropometrics				
Body mass index		25.1 ± 5.3	25.4	14.1-34.4
Overweight WHO cut-offs[1], n (%)		**Overweight SCI cut-offs[2], n (%)**		
9 (36)		4 (16)		
Obesity WHO cut-offs[1], n (%)		**Obesity SCI cut-offs[2], n (%)**		
5 (20)		14 (56)		
	n (%)	Mean ± SD	Median	Min–Max
Waist circumference		101 ± 14	103	70-127
≥102 cm (men), ≥88 cm (women)[3]	14 (56)			
Lifestyle factors				
Smoking status				
Never-smoker	11 (44)			
Ex-smoker	12 (48)			
Current smoker	2 (8)			
Physical activity				
Sedentery leisure time[4]	13 (52)			
No regular, mild- to moderate intensity LTPA[5]	8 (32)			
Regular moderate-intensity LTPA[6]	4 (16)			
Regular heavy intensity LTPA[7]	0 (0)			

LTPA= leisure time physical activity
[1]World Health Organization cut-offs[157]
[2]Cut-offs suggested by Laughton et al.[157]
[3]Cut-offs associated with increased cardiovascular risk[158]
[4]Participation in mild-intensity LTPA less than 2 hrs/week
[5]Participation in mild- to moderate-intensity LTPA at least 4 hrs/week, but not on a regular basis
[6]Participation in moderate-intensity LTPA 2-3 hrs in total, at least 1–2 times a week and minimum duration of 30 mins on every occasion
[7]Participation in heavy intensity LTPA at least three times a week and minimum duration of 30 mins on every occasion

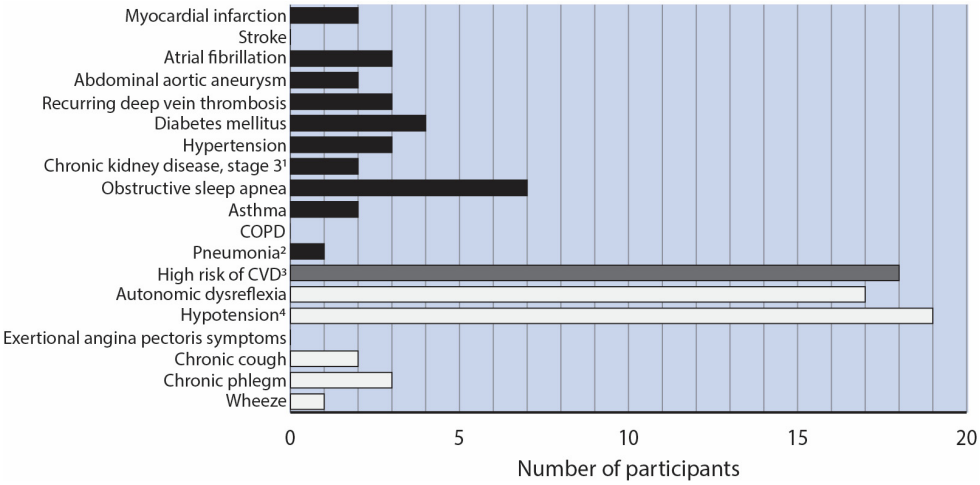


Figure 9. Comorbidities (black bars), cardiovascular risk (grey bar), and self-reported secondary health conditions and cardiopulmonary symptoms (white bars) of the participants in SPICA

[1]Absolute glomerular filtration rate values (30–59 ml/min/1.73 m2).

[2]Requiring hospitalization in the past 5 years

[3]Classified based on the occurrence of at least one of the following: waist circumference above cut-off levels, previous atherosclerotic disease, diabetes mellitus, chronic kidney disease, or SCORE >5

[4]I.e., a score >0 on item 1 of the hypotension part of the ADFSCI (any symptoms of dizziness, light headedness, blurred vision, nausea, weakness, confusion, fatigue, or passing out during the day)

ADFSCI= Autonomic dysfunction following spinal cord injury[1]; COPD= chronic obstructive pulmonary disease; CVD= cardiovascular disease

Descriptive findings of cardiopulmonary function and structure, and comparison with matched control data

Characteristics of the participants and the matched controls

In Table 8, the characteristics of the participants with SCI and the matched controls, and conditional regression analyses of Study II-IV are presented, based on the purpose of each study. The participants had significantly lower SCORE values, total cholesterol, non-HDL cholesterol, glucose and BMI, and significantly higher CRP. The lower total cholesterol and non-HDL cholesterol remained significant ($p<0.001$ and $p=0.009$, respectively) when analysing participants and controls ($n=19$ and $n=84$, respectively) not using lipid lowering medications.

Table 8. Characteristics of the participants with SCI and the matched controls, and conditional regression analyses of Study II-IV

	Participants with SCI n=25	Controls Study II n=125	Controls Study III n=125	Controls Study IV n=100
	n (%); Mean ± SD; Median, Min–Max			
Age	58 ±5; 58, 50–65	58 ±4; 57, 50-65	58 ±4; 57, 51-65	58 ±4; 58, 50-64
Smoker	2 (8)	19 (16)	12 (10)	8 (8)
Pack years[1]	8 ±11; 4, 0-46	17 ±30; 2, 0-154	17 ±31; 2, 0-151	12 ±20; 5, 0-140
CVD event	2 (8)		5 (4)	
Diabetes	4 (16)	5 (4)	4 (3)	
SCORE	2.1 ±1.4; 2, 0-6		2.8 ±2.0; 2, 0-11*	
COPD	0 (0)			0 (0)
Asthma	2 (8)			4 (4)
Cholesterol (mmol/L)	4.3 ±0.71; 4.2, 2.6-5.7		5.3 ±0.67; 5.2, 3.5-8.3**	
Non-HDL cholesterol (mmol/L)	3.1 ±0.71; 3.0, 1.9-4.4		3.8 ±1.0; 3.7, 2.2-6.7**	
Glucose[2] **(mmol/L)**	5.9 ±2.6; 5.3, 4.3-17.5		5.8 ±0.78; 5.7, 4.2-9.4**	
CRP[2] **(mg/L)**	5.1 ±7.2; 2.6, 0.0-31.0		2.0 ±2.4; 1.1, 0.6-16.0**	
Systolic BP (mmHg)	122 ±16; 121, 97-166	126 ±16; 123, 98-185	122 ±15; 121, 91-165	
Diastolic BP (mmHg)	75 ±9; 73, 55-95	77 ±9; 77, 58-104	74 ±9; 75, 53-95	
BMI (kg/m^2)	25.1 ±5.3; 25.4, 14.1-34.4	27.3 ±4.2; 26.7, 15.4-37.6*	27.7 ±4.4; 27.5, 17.5-43.9**	27.4 ±3.9; 26.9, 19.2-39.6*
WC (cm)	101 ±14; 103, 70-127	98 ±13; 99, 63-130	99 ±13; 99, 68-135	97 ±12; 96, 72-129
Height (cm)	175 ±8; 175, 160-190			175 ±8; 175, 149-191

BMI= body mass index; BP= blood pressure; COPD= chronic obstructive pulmonary disease; CRP= C-reactive protein; CVD= cardiovascular disease; HDL= high-density lipoprotein; SCORE= Systematic Coronary Risk Evaluation; WC= waist circumference

[1]One pack years is defined as smoking 20 cigarettes (or equivalent consumption of cigar or pipe) each day for a whole year.

[2]Mann-Whitney U test due to skewed data

*Significant at the 0.05-level (conditional logistic regression or Mann-Whitney U test)

**Significant at the 0.01-level (conditional logistic regression or Mann-Whitney U test)

Cardiovascular function and structure

Cardiovascular function

In Figure 10 and 11 and Table 9, descriptive findings of cardiac function and comparison with matched control data are presented. DBT was used to assess the parasympathetic autonomic response causing respiratory sinus arrythmia. HRV assessments using the DBT were significantly lower among the participants than the controls, except for heart rate and RMSSD. These results indicate that the cardiovagal function is impaired among the participants.

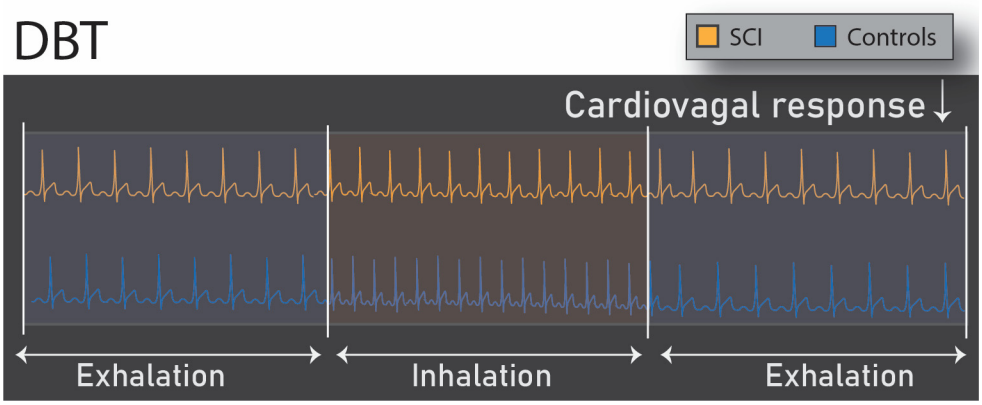


Figure 10. Deep breathing test of the participants in SPICA and matched controls
The DBT results schematically depicted where the differences in heart rate between inhalation and exhalation are measured. These differences were significantly lower among the participants with SCI indicating cardiovagal impairment.

The 24 hrs Holter ECG assessments demonstrated among the participants a significantly lower mean maximum heart rate, lower SDNN and a reduced LF/HF ratio between day and night than the controls. Among the participants, the mean difference between day and night LF/HF ratios was significant (-0.48; 95% CI: -0.9, -0.05).

These results indicate impaired sympathetic activity among the participants as SDNN, reflects both parasympathetic and sympathetic activity, whereas RMSSD (not significantly different) reflect parasympathetic activity. LF power may be produced by both parasympathetic and sympathetic activity whereas HF power mainly reflects parasympathetic activity. LF/HF ratio can then be used to assess the sympatho-vagal balance. The key result is that the circadian pattern is different between the participants and controls. During the night HF power may increase causing a lower LF/HF ratio.[12] Among the participants the case is the opposite with significantly higher LF/HF ratios during the night than day.

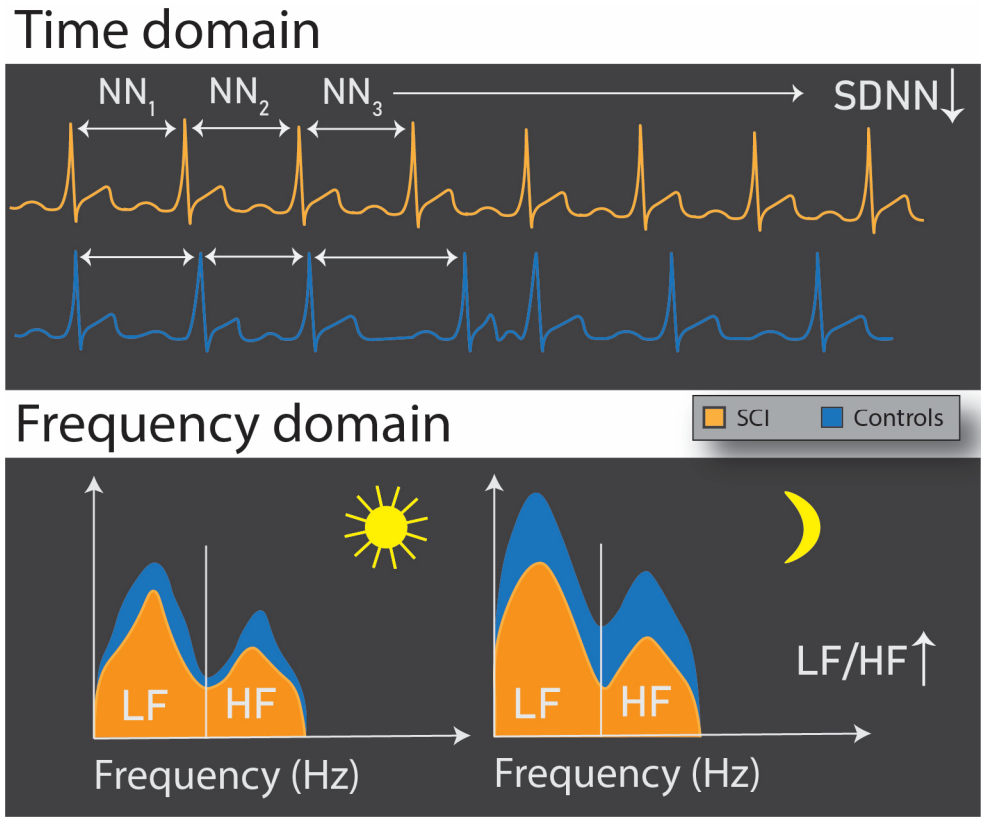


Figure 11. 24 hrs HRV assessments of the participants in SPICA and matched controls
The results of the 24 hrs HRV assessments are schematically depicted. SDNN was significantly lower i.e., the variability between heart beats was decreased among the participants compared with controls. LF/HF ratios were significantly higher among the participants during the night compared with day. Both LF and HF power measures (area under the curve) were higher during the night than day in participants and controls but among the participants with SCI the increase in LF was relatively greater than in HF causing the increase in LF/HF ratio.
HF= high frequency; HRV= heart rate variability; LF= low frequency; SDNN= standard deviation of the normal-to-normal interval

In Table 10, descriptive findings of vascular function and comparison with matched control data are presented. Diastolic orthostatic blood pressure increase was significantly lower among the participants than the controls (2.0 vs 9.4 mmHg; $p<0.001$). Five participants (20%) and two controls (2%) were classified as having orthostatic hypotension (OR=11; 95% CI: 2-59). The participants had significantly lower mean systolic and diastolic blood pressure measures, whereas the systolic standard deviation of blood pressure was significantly higher except during the night, compared with controls (illustrated in Figure 12). A reverse-dipper circadian blood pressure pattern occurred in ten (42%) and eight (7%) of the participants and controls, respectively (OR=8; 95% CI: 3-23).

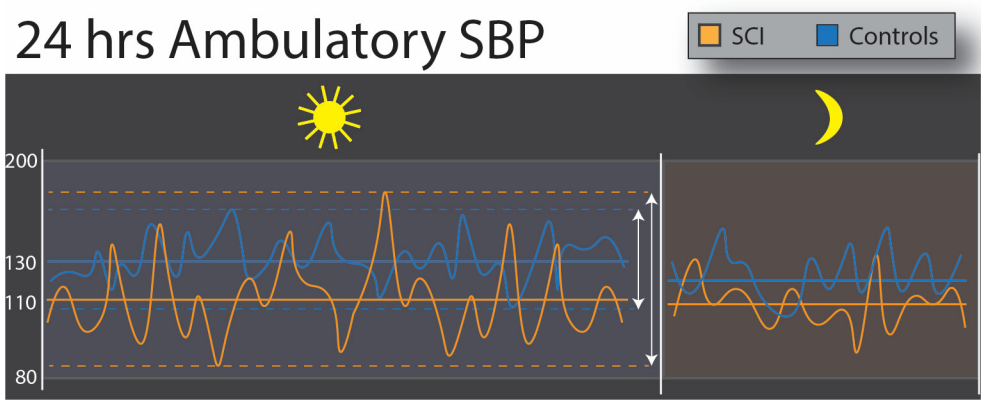


Figure 12. 24 hrs Ambulatory systolic blood pressure assessments of the participants in SPICA and matched controls
The mean SBP values (straight lines) and SBP variability (curved lines) schematically depicted. Mean SBP values were significantly lower both during day and night in participants with SCI. SBP variability was significantly increased (arrowed lines) among participants with SCI compared with controls, in particular during daytime. SBP variability during the night was lower with no significant differences between participants and controls.
SBP= systolic blood pressure

These results indicate that, among the participants, the orthostatic blood pressure response mediated by sympathetic activity is impaired. Blood pressure during 24 hrs is lower on the average but the systolic blood pressure is fluctuating, especially during daytime, as compared with controls. Finally, a nocturnal blood pressure rise was significantly more often occurring among the participants than controls.

Table 9. Descriptive findings of cardiac function and comparison with matched control data using conditional regression analyses

	Participants with SCI n=25		Controls n=125		Odds ratio[1] 95% CI	p-value
Deep breathing test[2]	Mean ±SD; Median, Min–Max					
HR (bpm)	65 ±11; 64	45-89	64 ±10; 64	43-86	1.0 (0.96-1.05)	0.86
E-I$_{median}$ (bpm)	6.9 ±4.7; 4.9	1.6-20.6	10.3 ±6.3; 8.9	1.1-32.5	0.87 (0.77-0.97)	**0.017**
E/I (bpm)	1.12 ±0.09; 1.09	1.02-1.47	1.18 ±0.12; 1.14	1.01-1.57	0.0 (0.0-0.34)	**0.023**
E-I$_{mean}$ (bpm)	7.9 ±5.1; 6.8	2.0-20.9	11.2 ±6.1; 10.1	1.5-29.7	0.88 (0.79-0.98)	**0.017**
SD$_{HR}$ (bpm)	3.3 ±1.9; 3.0	0.8-8.2	4.5 ±2.5; 4.0	0.5-14.4	0.75 (0.58-0.97)	**0.028**
MCR	1.3 ±0.9; 1.0	0.05-3.3	2.1 ±1.3; 1.8	0.21-6.8	0.43 (0.24-0.79)	**0.006**
RMSSD (ms)	39 ±40; 30	7-204	53 ±39; 41	5-200	0.99 (0.98-1.0)	0.14
24 hrs Holter[3]						
Mean HR (bpm)	73 ±12; 73	49-101	76 ±10; 77	51-102	0.96 (0.92-1.01)	0.12
Mean minimum HR (bpm)	51 ±9; 49	37-65	51 ±7; 50	33-74	1.00 (0.94-1.06)	1.0
Mean maximum HR (bpm)	116 ±21; 113	76-157	140 ±18; 142	101-183	0.92 (0.89-0.96)	**<0.001**
SDNN (ms)	112 ±34; 113	55-172	145 ±38; 143	56-262	0.97 (0.96-0.99)	**<0.001**
RMSSD (ms)	23 ±11; 22	8-53	27 ±12; 24	9-74	0.97 (0.93-1.02)	0.23
HF$_{day}$ (ms^2)	860 ±1000; 594	125-5034	1073 ±896; 804	62-4962		0.31
HF$_{night}$[4] (ms^2)	1163 ±1226; 687	19-4986	1630 ±1587; 1152	34-9780		0.06
LF$_{day}$[4] (ms^2)	2112 ±3421; 1423	118-17562	2268 ±1464; 2161	101-7661		0.10
LF$_{night}$ (ms^2)	2946 ±3103; 2030	65-11280	3178 ±2252; 2881	91-11725		0.66
LF/HF$_{day}$	2.4 ±1.1; 2.4	0.61-4.9	2.5 ±0.94; 2.4	0.72-5.5	0.84 (0.49-1.42)	0.51
LF/HF$_{night}$	2.9 ±1.7; 2.2	0.38-6.2	2.5 ±1.3; 2.3	0.63-7.5	1.25 (0.88-1.76)	0.21
LF/HF$_{day}$ -LF/HF$_{night}$	-0.48 ±1.0; -0.33	-3.2-1.1	0.008 ±0.87; 0.10	-3.2-2.9	0.54 (0.32-0.92)	**0.023**

E-I=expiration-inspiration difference; E/I= expiration-inspiration ratio; HF=high frequency; HR= heart rate; LF= low frequency; MCR= mean circular resultant; RMSSD= root mean square of successive differences; SD$_{HR}$= standard deviation of heart rate; SDNN= standard deviation of the NN interval

[1]The odds ratios of the continuous variables implicate the odds of being a participant with SCI for a one-unit increase in the variable

[2]Number of participants and controls 25 and 103, respectively

[3]Number of participants and controls 24 and 114, respectively

[4]Conditional logistic regression computed on transformed data due to skewness

Table 10. Descriptive findings of vascular function and comparison with matched control data using conditional regression analyses

	Participants with SCI n=25		Controls n=125		Odds ratio[1] 95% CI	p-value
Orthostatic blood pressure[2]	n (%); Mean ±SD; Median, Min–Max					
Difference in systolic BP (mmHg)	0.08 ±16; 3	-29-26	2.5 ±11; 2.5	-48-28	0.98 (0.94-1.02)	0.37
Difference in diastolic BP (mmHg)	2.0 ±10; 2.0	-29-21	9.4 ±7; 10	-18-24	0.89 (0.83-0.95)	**<0.001**
Orthostatic hypotension	5 (20)		2 (2)		11 (2-59)	**0.004**
Ambulatory blood pressure[3]						
Mean systolic BP (mmHg)	111 ±14; 111	90-145	125 ±11; 125	101-159	0.89 (0.84-0.94)	**<0.001**
Mean systolic BP_{day} (mmHg)	112 ±15; 109	95-148	129 ±12; 128	106-158	0.89 (0.84-0.94)	**<0.001**
Mean systolic BP_{night} (mmHg)	108 ±16; 108	78-140	117 ±12; 117	86-161	0.95 (0.91-0.98)	**0.005**
Mean diastolic BP (mmHg)	67 ±8; 66	50-90	77 ±8; 76	56-100	0.84 (0.77-0.91)	**<0.001**
Mean diastolic BP_{day} (mmHg)	68 ±9; 67	51-94	80 ±9; 79	57-102	0.83 (0.77-0.91)	**<0.001**
Mean diastolic BP_{night} (mmHg)	63 ±9; 64	48-83	70 ±9; 69	51-98	0.92 (0.87-0.97)	**0.004**
Systolic SD_{BP} (mmHg)	17.8 ±4.7; 18.1	11.9-28.9	15.7 ±4.5; 15.5	6.5-30.5	1.13 (1.01-1.26)	**0.029**
Systolic $SD_{BP\ day}$ (mmHg)	17.6 ±5.0; 16.9	9.2-28.8	12.2 ±5.0; 13.7	5.7-30.9	1.14 (1.04-1.25)	**0.006**
Systolic $SD_{BP\ night}$ (mmHg)	13.4 ±6.0; 12.0	5.2-26.9	11.6 ±4.9; 11.2	3.1-30.5	1.06 (0.98-1.15)	0.13
Diastolic SD_{BP} (mmHg)	12.4 ±3.0; 12.5	4.9-19.1	12.6 ±3.5; 12.3	5.8-23.0	0.98 (0.86-1.12)	0.86
Diastolic $SD_{BP\ day}$ (mmHg)	12.0 ±3.2; 11.8	4.7-18.2	11.1 ±4.3; 10.2	2.9-24.5	1.05 (0.95-1.17)	0.33
Diastolic $SD_{BP\ night}$ (mmHg)	9.5 ±3.8; 8.2	4.1-19.6	9.1 ±3.5; 8.6	1.9-19.6	1.02 (0.91-1.16)	0.64
Dipper	5 (21)		47 (42)		0.37 (0.13-1.1)	0.07
Extreme-dipper	1 (4)		5 (5)		0.88 (0.10-8.1)	0.91
Non-dipper	8 (33)		52 (46)		0.56 (0.22-1.42)	0.22
Reverse-dipper	10 (42)		8 (7)		8 (3-23)	**<0.001**

BP= blood pressure; SD_{BP}= standard deviation of blood pressure

[1]The odds ratios of the continuous variables implicate the odds of being a participant with SCI for a one-unit increase in the variable

[2]Number of participants and controls 25 and 112, respectively

[3]Number of participants and controls 24 and 117, respectively. Night measures were missing in five additional controls.

Cardiovascular structure

In Table 11, descriptive findings of cardiovascular structure and comparison with matched control data are presented. Among the participants 44% exhibited coronary and carotid plaques, whereas 67% of the controls exhibited coronary plaques and 59% exhibited carotid plaques. The mean coronary artery calcium score in the participants and controls, were 134 (min-max 0-1436) and 99 (min-max 0-5034), respectively. Scores >100 occurred in 18% and 21%, in participants and controls respectively. No significant differences were shown regarding the atherosclerosis variables between participants and controls. IMT in the carotid bulb was significantly lower among the participants than the controls.

Conditional logistic regression analyses were also adjusted for the CVD risk factors using SCORE values and the OR (95% CI) comparing participants vs controls were: Coronary artery calcium score >0 (OR=0.57; 95% CI: 0.23-1.47), any carotid plaque (OR=0.46; 95% CI: 0.18-1.19) and IMT in the carotid bulb (OR per 1 mm increment=0.06; 95% CI: 0.003-0.98).

The cardiovascular structure was assessed using imaging in order to measure the atherosclerotic burden and IMT. The results indicate that atherosclerosis is not increased among the participants. This is possibly not solely due to the lower CVD risk assessed with SCORE, as the non-adjusted and adjusted results did not differ considerably. The surrogate marker for atherosclerosis, IMT in the carotid bulb, was significantly lower indicating reduced cardiovascular structural impairment and risk for CVD.

In summary, several cardiovascular functional impairments and disordered circadian patterns were observed among the participants with SCI compared with controls indicating worse cardiovascular health. On the contrary, cardiovascular structural impairments were not increased or even better in participants with SCI than controls.

Table 11. Descriptive findings of cardiovascular structure and comparison[1] with matched control data

	Participants with SCI n=25		Controls n=125		Odds ratio[2] 95% CI	p-value
Coronary CT Angiography[3]	n (%); mean ±SD; median, min-max)					
Any atherosclerosis	7 (44)		49 (67)		0.38 (0.13-1.17)	0.093
Segment involvement score	1.0 ±1.6; 0	0-6	2.1 ±2.5; 1.00	0-11	0.74 (0.52-1.06)	0.098
Coronary artery calcium score[4]						
>0	10 (44)		66 (59)		0.52 (0.21-1.31	0.17
1-100	6 (26)		43 (38)			
>100	4 (18)		23 (21)		0.61 (0.16-2.3)	0.47
Carotid ultrasound[5]						
Any plaque	10 (44)		68 (59)		0.54 (0.22-1.32)	0.18
Total plaque area (mm^2)[6]	18±7.8; 17	8-36	31±32.1; 25	3-237		0.093
Mean IMT carotid bulb (mm)	0.78±0.12; 0.74	0.58-1.09	0.91±0.31; 0.86	0.44-3.02	0.05 (0.003-0.80)	**0.034**
Mean IMT CCA (mm)	0.68±0.10; 0.69	0.45-0.88	0.70±0.15; 0.68	0.45-1.28	0.18 (0.003-9.31)	0.39

CCA= common carotid artery; CT= computed tomography; IMT= intima media thickness

[1]Conditional logistic regression

[2]The odds ratios of the continuous variables implicate the odds of being a participant with SCI for a one-unit increase in the variable

[3]Number of participants and controls 16 and 73, respectively

[4]Number of participants and controls 23 and 108, respectively

[5]Number of participants and controls 23 and 115, respectively

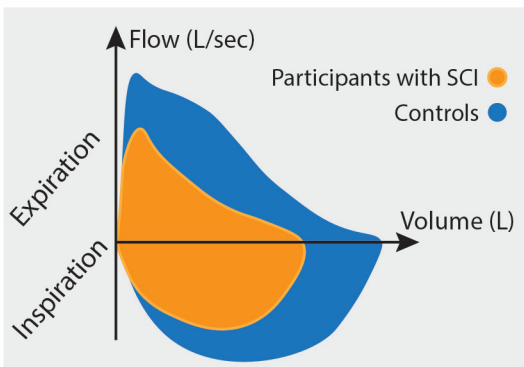
[6]Comparison using Mann-Whitney U test due to skewed data

Pulmonary function and structure

Pulmonary function

In Figure 13, the results of the spirometry and diffusing capacity of the participants and matched controls are presented. All variables were significantly lower among the participants with SCI except for FEV_1/FVC.

	Participants with SCI	Controls
	mean ±SD; median, min-max	mean ±SD; median, min-max
VC	69 ±21; 70, 30-106	107 ±14; 108, 63-150
FEV_1	70 ±24; 71, 33-111	109 ±15; 108, 69-148
FEV_1/FVC	0.8 ±0.1; 0.8, 0.5-0.9	0.8 ±0.05; 0.8, 0.6-0.9
MEF_{50}	65 ±30; 66, 17-115	100 ±30; 97, 27-164
D_{LCO}	64 ±20; 65, 26-115	93 ±12; 93, 63-117
k_{CO}	90 ±22; 84, 38-130	100 ±14; 100, 71-129



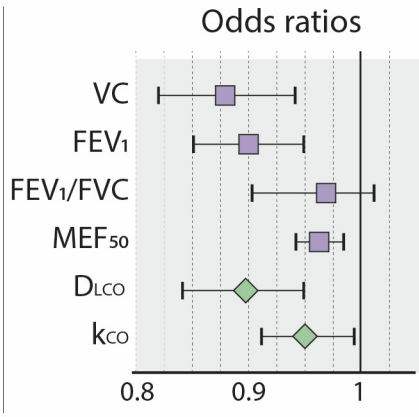


Figure 13. Pulmonary function assessed with spirometry and diffusing capacity for the participants with SCI and controls

All values represent predicted percent of the functional variable. Odds ratios represent the odds of being a participant with SCI for a one percent increment in the variable (the shapes in the center are the ORs and the bars the 95% CI). The spirometry patterns are schematically depicted. CO= carbon monoxide (ml/(min kPa L)); D_{LCO}= diffusing capacity of the lungs for carbon monoxide (mmol/(min kPa)); FEV_1= forced expiratory volume in 1 s; FVC= forced vital capacity; k_{CO}= Carbon monoxide transfer coefficient (ml/(min kPa L)); MEF_{50}= maximal expiratory flow at 50%; SVC= slow vital capacity; V_A= Alveolar volume (L); VC= vital capacity

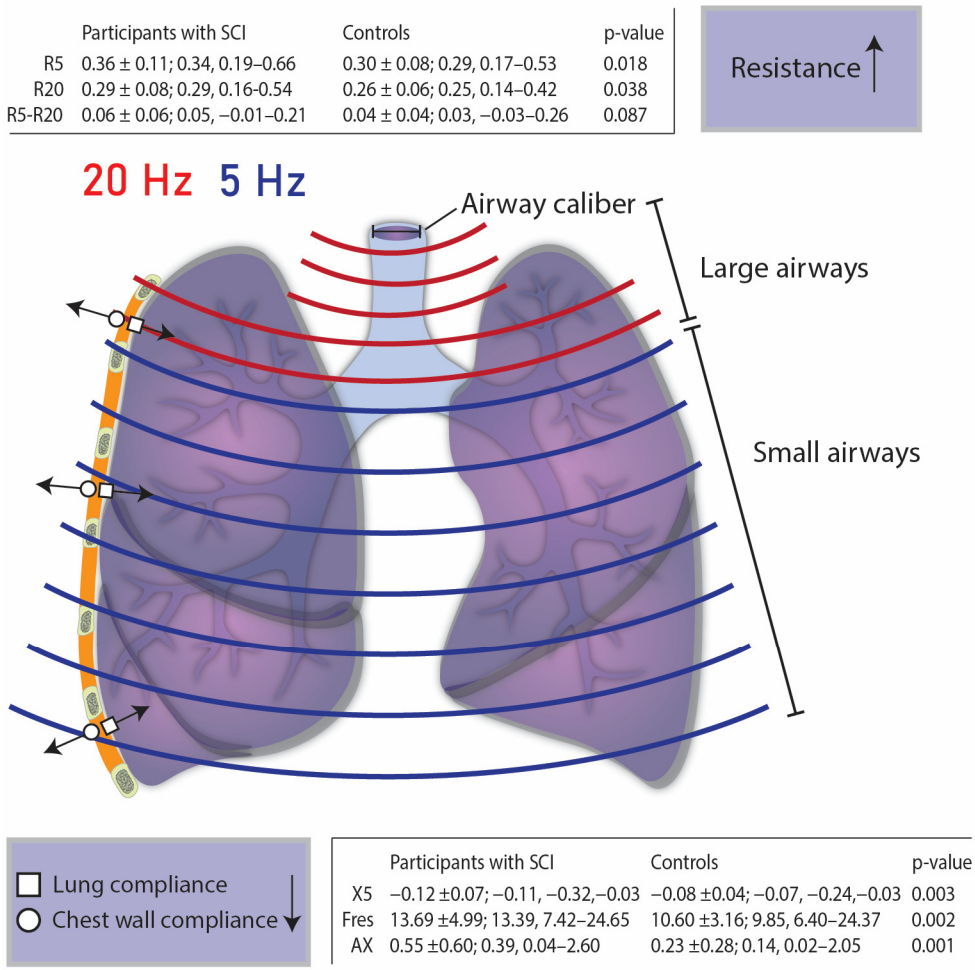
The spirometry and diffusing capacity both illustrate pulmonary functional impairments among the participants. Both FEV_1 and FVC are lower among the participants and so the FEV_1/FVC ratio indicating airway obstruction is not significantly different than the controls.

In Figure 14, the results of the IOS for the participants and matched controls are presented. All variables except R5-R20 were significantly different between participants and controls. The IOS results indicate increased total airway resistance and large airway resistance (R5 and R20) and an increased stiffness of the pulmonary system (X5, Fres and AX) among the participants with SCI.

Pulmonary structure

In Figure 15, descriptive findings of pulmonary structure and the comparison with matched control data are presented. Structural impairments were frequently occurring among both participants and controls and there were no significant differences between the groups. The most common structural impairment among the participants was linear scars of atelectasis (n=13; 54%). These results indicate that pulmonary structural impairments are not considerably different among the participants with SCI than the controls.

	Participants with SCI	Controls	p-value
R5	0.36 ± 0.11; 0.34, 0.19–0.66	0.30 ± 0.08; 0.29, 0.17–0.53	0.018
R20	0.29 ± 0.08; 0.29, 0.16-0.54	0.26 ± 0.06; 0.25, 0.14–0.42	0.038
R5-R20	0.06 ± 0.06; 0.05, −0.01–0.21	0.04 ± 0.04; 0.03, −0.03–0.26	0.087



	Participants with SCI	Controls	p-value
X5	−0.12 ±0.07; −0.11, −0.32,−0.03	−0.08 ±0.04; −0.07, −0.24,−0.03	0.003
Fres	13.69 ±4.99; 13.39, 7.42–24.65	10.60 ±3.16; 9.85, 6.40–24.37	0.002
AX	0.55 ±0.60; 0.39, 0.04–2.60	0.23 ±0.28; 0.14, 0.02–2.05	0.001

Figure 14. Pulmonary function assessed with impulse oscillometry for the participants with SCI and controls.
Values presented as mean ±SD; median, min-max. Comparison using conditional logistic regression (AX on transformed data due to skewness). Airway resistance (R5 and R20) was significantly higher indicating increased resistance in both the large and small airways. X5 (kPa/(L/s)) reflects the elastic properties (elastance) of the pulmonary system at 5 Hz (i.e., lung periphery). Fres (Hz) is the frequency where inertance (inertive forces of the air column) and elastance are equal. AX is the area under the curve between 5 Hz and Fres reflecting elastance. The significantly lower X5, higher Fres and greater AX all indicate increased stiffness of the pulmonary system.
AX= reactance curve area below zero (kPa/L); Fres= resonant frequency (Hz); R20= resistance at 20 Hz (kPa/(L/s)); R5= resistance at 5 Hz (kPa/(L/s)); R5-R20= difference in resistance at 5 Hz and 20 Hz (kPa/(L/s)); X5= reactance at 5 Hz (kPa/(L/s))

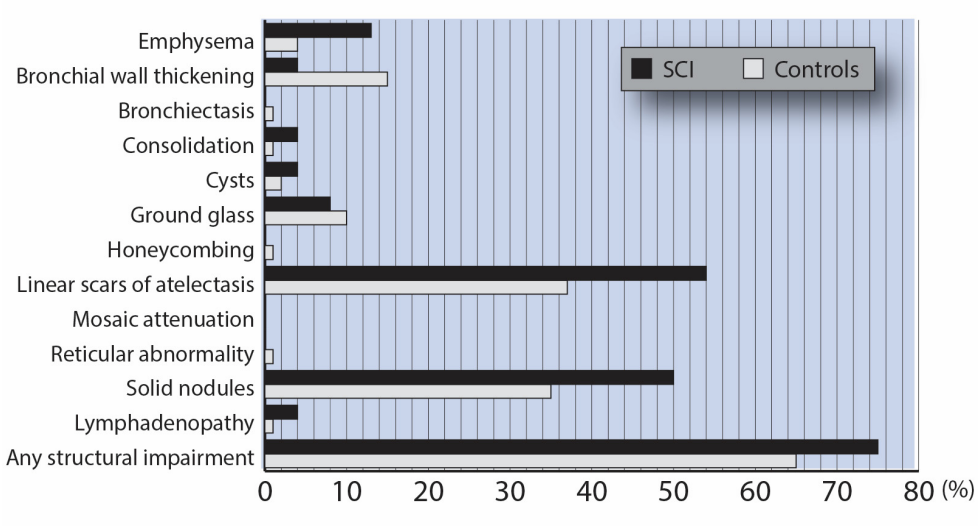


Figure 15. Descriptive findings of pulmonary structure and comparison with matched controls

Associations with injury level and age

Correlations between neurological level of injury and cardiopulmonary function and pulmonary structure

In Table 12, statistically significant Spearman's rank correlation coefficients (rho) between NLI and cardiopulmonary function and pulmonary structure are presented. Several cardiopulmonary functions were significantly associated with a more rostral NLI, whereas any pulmonary structural impairment was the only structural variable significantly associated with a more rostral NLI. These results were all indicating greater cardiopulmonary impairments with a more rostral NLI.

Associations between age and pulmonary structure

Older age was significantly and positively associated with the occurrence of linear scars of atelectasis among the participants (OR=1.3; 95% CI: 1.04-1.74). There was no such association among the controls (OR=0.9; 95% CI: 0.88-1.07). This difference between participants and controls was significant (p=0.025). There was no significant association between older age and any structural impairment among the participants or controls (OR=1.04 95% CI: 0.84-1.29 and OR=1.03 95% CI: 0.93–1.14, respectively).

Table 12. Spearman's rank correlation coefficient (rho) between neurological level of injury and cardiopulmonary function and pulmonary structure

Variable		rho	p-value
Neurological level of injury[1]	Cardiovascular function		
	Deep breathing test		
	Heart rate (bpm)	-0.40	0.048
	E-I_{mean} (bpm)	-0.42	0.037
	SD_{HR} (bpm)	-0.48	0.015
	MCR	-0.41	0.041
	24-hour Holter		
	Mean maximum HR (bpm)	-0.63	<0.001
	LF/HF_{day}	-0.53	0.008
	LF/HF_{night}	-0.45	0.028
	Blood pressure		
	Resting systolic BP (mmHg)	-0.40	0.048
	Ambulatory blood pressure		
	Systolic SD_{BP} day (mmHg)	0.46	0.030
	Pulmonary function		
	Spirometry		
	VC (% predicted)	-0.58	0.002
	FEV_1 (% predicted)	-0.57	0.003
	FEV_1/FVC	-0.53	0.007
	MEF_{50} (% predicted)	-0.64	0.001
	Impulse oscillometry		
	R5 (kPa/(L(s))	0.42	0.046
	Pulmonary structure		
	Any structural impairment	0.51	0.012

BP= blood pressure; E-I= expiration-inspiration difference; FEV_1= forced expiratory volume in 1 s; FVC= forced vital capacity; HF= high frequency; HR= heart rate; LF= low frequency; MCR= mean circular resultant; MEF_{50}= maximal expiratory flow at 50%; R5= resistance at 5 Hz; RMSSD= root mean square of successive differences; SD_{BP}= standard deviation of blood pressure; SD_{HR}= standard deviation of heart rate; SDNN= standard deviation of the NN interval; VC= vital capacity

[1]Defined as each more rostral neurological level of injury

In summary, NLI was related to several cardiopulmonary functional impairments and the presence of pulmonary structural impairments, indicating worse cardiopulmonary health with increasing NLI. Older age among the participants with SCI was related to the presence of atelectasis which was not the case among the controls.

Discussion

Cardiopulmonary diseases have emerged as the major causes of death in people with SCI. In the SCI population, the most vulnerable people are those with cervical and upper thoracic SCI, who have the lowest life expectancy. The studies comprising this thesis aimed to comprehensively describe and explore cardiopulmonary health in a population-based cohort of middle-aged people with long-term cervical and upper thoracic SCI and compare their health with matched controls from the general population. These studies provide a detailed clinical picture of cardiopulmonary health in this population. The results can be used to generate hypotheses for forthcoming research and highlight specific issues to improve the clinical management. The main findings are the presence of multiple functional impairments among the participants compared with controls, whereas structural impairments were not considerably different. Additionally, cardiopulmonary functional impairments were worse with a more rostral NLI.

In Figure 16, the cardiopulmonary results are summarized. Several results were expected from the knowledge base of neurologic deficits after SCI, whereas other results were less expected due to the epidemiology of SCI. Here, the results are first discussed in view of previous research. Then the results are discussed in view of the clinical management and avenues for future research.

Characteristics

Anthropometrics, lifestyle factors and medical history

The BMI and WC among the participants with SCI indicate considerable visceral adiposity, related to CVD risk and pulmonary impairment, in agreement with previous research.[61,73,159] Similarly, physical inactivity is a CVD risk factor which is frequent in people with SCI.[64,160] This is also in agreement with the results in this thesis, where most participants reported a sedentary leisure time. Current smoking was not common among the participants with SCI (n=2). Although non-significant, the controls had less favourable current smoker status and smoking history than the participants. In comparison with larger SCAPIS data this feature was consistent.[148] Previous research indicate that smoking prevalence reduces after a high pre-injury prevalence and is lower among people with more severe SCI.[161,162]

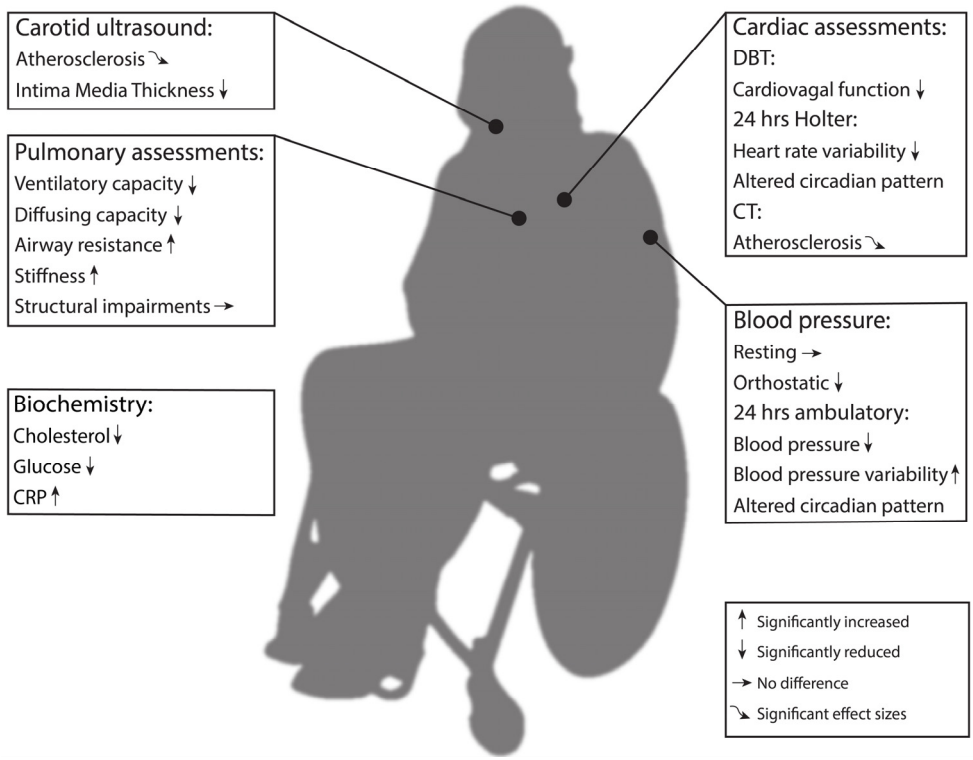


Figure 16. Summary of the major cardiopulmonary results of the participants with SCI compared with controls

Significant effect sizes refer to OR <0.54

CRP= C-reactive protein; CT= computed tomography; DBT= deep breathing test

Previous CVD event (n=2; 8%) was more common among the participants with SCI as compared with the general population. In SCAPIS, previous MI occurred in 1.6% and stroke in 1.4% of the participants.[148] In the control group, 4% had a previous event. A greater presence is expected among participants and controls as the proportion of men is higher.[163] These populations are small, and inferences cannot be drawn but the results are consistent with previous research of greater CVD prevalence in SCI.[164] The high occurrence of comorbidities (diabetes, dyslipidaemia, chronic kidney disease and obstructive sleep apnea), associated with CVD risk, among the participants with SCI is also consistent with previous research.[60,62,63,95,165] After the data collection, one additional third of the participants were diagnosed with obstructive sleep apnea due to self-reported symptoms requiring further investigations. Hypertension occurred less frequently, which can be linked to the autonomic dysfunction in cervical and upper thoracic SCI.[45]

Cardiovascular risk was classified as high in nearly three quarters of the participants due to the presence of risk factors (WC, diabetes mellitus, kidney function,

established CVD, or SCORE). However, the estimated CVD risk based on SCORE was significantly lower among the participants with SCI than controls due to lower cholesterol levels (discussed below) indicating a lower CVD risk.

None of the participants with SCI reported symptoms of exertional angina pectoris. Further, CCTA and medical follow-up identified one participant with significant stenosis and thus a great occurrence of these symptoms is not anticipated. Symptoms of cardiovascular autonomic impairment occurred frequently (AD 68% and hypotension 76%, respectively). The AD occurrence was slightly higher than in a comparable study reporting 57%.[166] Indwelling urinary catheter blockage in one participant caused AD and a myocardial infarction. This serious risk of AD in people with SCI has been previously described.[167] Hypotensive symptoms are, although frequent, unspecific and may not be related to autonomic impairment *per se*. The medications of the participants revealed an exposure to numerous medicines with anticholinergic effects (see Appendix). Common adverse effects of these are similar to the reported hypotensive symptoms and may contribute to the results.[168]

The occurrence of asthma (n=2; 8%) and COPD (n=0) were to some extent in line with the study by Stolzmann et al.[169] who reported asthma in 10%, and COPD in 9%, respectively. Data in that study were collected during 1994-2005 and smoking occurred in 21%, which may explain the COPD differences.[169] The occurrence of chronic cough (8% vs 17%), chronic phlegm (12% vs 21%) and wheeze (4% vs 50%) were accordingly greater in that study.[169] The same pattern of greater occurrence of smoking and pulmonary symptoms was reported by Spungen et al. (1997).[170]

Retrospective data of pneumonia requiring hospitalization revealed one case in 125 person years (45-65 years of age). Comparable pneumonia incidence data in SCI are not available. In the general population, the incidence of hospitalization due to pneumonia is low in middle-age and rapidly increases in old age.[94] This case was at the age of 62 years and therefore consistent with the general population incidence.[94]

Biochemistry

Cholesterol levels were significantly lower than controls which has been reported in the literature.[62] The reductions are greater in people with cervical NLI.[62] Due to the role of cholesterol in atherosclerosis pathophysiology this characteristic is important.[171] In recent years, emphasis on the different lipid parameters has deviated. HDL cholesterol, being considered protective, has not been shown to have a causal effect and is instead considered an inverse marker of the atherogenic non-HDL cholesterol.[172] Therefore, the general reduction of cholesterol levels in cervical SCI may indicate an important protective factor for CVD. There are data suggesting that lower cholesterol levels in SCI is due to interrupted sympathetic activity to the liver which affect the liver lipid metabolism.[173,174]

The lower fasting glucose levels among the participants with SCI is another important characteristic, as the relationship between fasting glucose and CVD has been reported to have a J-shaped appearance.[175] It has been hypothesized that low fasting glucose levels is indicative of glycemic variability which is associated with CVD risk.[175] Among the participants, the fasting glucose levels were reversed J-shaped, i.e., a majority were distributed in the lowest quartile and a few, contributing substantially to the mean values, in the highest quartile. This distribution may indicate that the participants expressed a greater risk despite lower total values, as few of the participants were distributed in the average span. Glycemic variability can be interpreted from previous research in SCI.[176-178] Impaired oral glucose tolerance but essentially normal fasting glucose levels have been reported.[176-178] The higher glucose levels in some participants were due to present diabetes mellitus.

Increased CRP is consistent with previous SCI research.[179] CRP is related to CVD as a marker for the low-grade inflammation of the metabolic syndrome, in turn caused by ectopic fat distribution.[180] CRP is a non-specific biomarker and therefore other factors, for example pressure injuries and use of urinary catheter (both occurring in six of the participants, respectively), are likely to contribute to the finding. Thus, the increased levels are not interpreted as increased ectopic fat specifically among the participants. Despite that, the elevated CRP indicate inflammation and may therefore be indicative of a prothrombotic milieu.[181]

In summary, the characteristics of the SPICA cohort do not stand out in relation to previous research. Therefore, the population-based sample, despite being small, is seemingly representative. Some characteristics indicate a worse cardiopulmonary health (e.g., visceral adiposity) whereas other indicate the opposite (e.g., low cholesterol levels). CVD risk factors are common, but the estimated CVD risk is lower than in the general population.

What is known, what is new?

Cardiovascular function and structure

In this thesis, eight different assessments provided a novel, broad and in-depth description of cardiovascular function and structure. Cardiovascular function indicated a reduced cardiovagal response and alterations in sympatho-vagal balance and circadian pattern. Some functional impairments were worse in relation to a more rostral NLI. Structural impairments of the coronary and carotid arteries were not increased, and sometimes even better among participants with SCI than controls.

Cardiovascular function

Among the participants with SCI compared to the controls, cardiovagal response and 24 hrs SDNN were reduced, and an increase in LF/HF ratio during the night occurred. These results indicate reduced parasympathetic activity, sympathetic activity, and sympatho-vagal balance, respectively. ABPM revealed lower blood pressure, increased blood pressure variability and frequent nocturnal blood pressure rise. NLI was related to several of the cardiovascular functional impairments (i.e., worse with a more rostral NLI).

One previous study[97] has reported DBT results in SCI (ten inpatient participants, mean age 36 years and compared with data from 20 controls collected years earlier). Nevertheless, these results did not differ compared with this thesis as the authors reported significant differences indicating a decreased cardiovagal response.[97]

There are five studies[98-102] providing results from 24 hrs HRV assessments in SCI, of which three[98-100] are comparable with this thesis but in younger populations. Two studies[98,99] reported comparable results, lower SDNN but not RMSSD, as in this thesis whereas the last[100] did not report any significant time domain differences. Lower SDNN can be expected as it corresponds to both parasympathetic and sympathetic activity as the latter is impaired in this population.[12]

One study reported increased LF/HF ratios in participants with tetraplegia compared to paraplegia.[98] This contrasts with this thesis as LF/HF was negatively correlated with higher NLI. This may be due to the comparison with low paraplegia in that study[98] as these NLIs are less affected by cardiovascular autonomic impairments. That study demonstrated a greater LF/HF ratio in the participants with tetraplegia during the night than day in agreement with the altered circadian pattern in this thesis.[98]

In conclusion, very little is known about cardiovagal response to deep breathing and 24 hrs HRV in SCI, and previously completely missing in middle-aged people many years after injury. Therefore, the HRV must be interpreted by comparing with the general population where reduced HRV is a CVD risk factor.[12] Levels of SDNN

below 100 are indicative of compromised health.[12] Pathophysiological links to dysrhythmias, metabolic abnormalities as well as to directly influencing the progression of atherosclerotic plaques have been reported.[147]

HRV is modulated by different factors in the shorter and longer term.[12] Ventilation, baroreflexes and renin-angiotensin-aldosterone-system contribute to HRV and are all factors that are known to be affected by the SCI.[43,182,183] Future research therefore need to determine what factors contribute to reduced HRV in SCI and whether these impairments are prognostically significant.

The relationships between NLI and several of the DBT and 24 hrs HRV parameters are also new and noticeable. The results can be expected due to the segmental organization of the cardiopulmonary innervation. However, it does not point in the direction of the origin of the lower HRV as both cardiovascular (sympathetic activity) and pulmonary innervation (ventilatory capacity) is reduced in relation to a more rostral NLI in this population.

Furthermore, the differences in circadian pattern of HRV are noteworthy but the pathophysiology is uncertain. Is it due to hemodynamic changes and an increase in nocturnal blood pressure affecting baroreceptors?[12,47,183] Or is it influenced by the sleep disordered breathing which may cause differences in sleep stages?[184,185] The altered respiratory mechanics in the seated vs supine position may also influence HRV differences between day and night. In the general population, CVD events are more common in the morning which has been suggested to be linked to the cardiovascular circadian pattern.[185] Thus, does this feature have a prognostic impact in people with SCI?

Finally, some hypotheses can be formulated based on the effect sizes and significance levels: are LF_{day} and HF_{night} power lower in people with cervical and upper thoracic SCI than controls (significance level 90% and 94%, respectively)?

The 24 hrs ABPM results in this thesis are in agreement with previous studies of younger study populations demonstrating overall lower mean blood pressure, increased blood pressure variability and decreased nocturnal blood pressure dip in cervical and upper thoracic SCI, and more pronounced in cervical SCI.[55,99,103-109] The discrepancies between resting blood pressure and 24 hrs ABPM may indicate the usefulness of the latter when evaluating baseline blood pressure in people with SCI.

Orthostatic hypotension has been assessed in the acute phase of SCI but rarely in the chronic phase.[110-113] Four comparable studies reported a greater occurrence of OH in, overall, younger study populations of long-term cervical and upper thoracic SCI (23%,[110] 32%,[111] 33%[112] and 47%,[113] respectively) than in this thesis (20%). The greater occurrence may be due to shorter time since injury in these studies, as the orthostatic response in SCI is considered to stabilize over time.[182]

Orthostatic hypotension and the reverse-dipper pattern are CVD risk markers in the general population but the prognostic significance in SCI is unclear.[59,186] What

contributes to the reverse-dipper pattern? Hemodynamic changes between the seated and supine position[47] and sleep disordered breathing[96] are two factors that affect blood pressure which may contribute to this result.

Cardiovascular structure

In this thesis, coronary atherosclerosis in SCI was assessed for the first time with CCTA and the second time with coronary artery calcium and demonstrates no increase in atherosclerotic burden. A greater focus in the literature has been on risk factors for CVD than CVD prevalence itself.[164] Therefore, the atherosclerosis imaging results are considered the most important findings.

The coronary artery calcium study[114] comprising 91 people (mean age 50 years) with cervical and thoracic SCI and 273 controls, scarcely reported the methodology limiting comparison. For example, injury aetiology and matching criteria were not reported.[114] Undefined matching of controls for CVD risk factors may explain the higher occurrence of coronary artery calcium in that study as compared with controls (51% and 39%, respectively) than in this thesis (44% and 59%, respectively).[114] If matching for BMI and cholesterol levels occurred this is likely to cause a control group with another characteristic (less visceral adiposity and atherogenic lipids), explaining the difference. Moreover, cervical SCI was related to a greater atherosclerotic burden in contrast with the results in this thesis. Participants with cervical SCI in that study[114] possibly have more reduced BMI and atherogenic lipids. Therefore, the speculative explanation of matching criteria to the difference is consistent.

Ultrasound was used to assess carotid atherosclerosis and carotid IMT and demonstrated no increase in atherosclerotic burden and lower carotid IMT in the bulb and similar in the common carotid artery. One study[115] has reported carotid atherosclerosis previously whereas IMT has been assessed in younger people with SCI, and mostly in male populations.[114] The previous study[115] of carotid atherosclerosis reported plaque score results in 57 men with cervical and upper thoracic SCI (mean age 40 years) and compared with 62 men from the general population. Atherosclerotic plaques occurred less frequently (30% in participants and 26% in controls, respectively) than in this thesis (44% and 59%, respectively).[115] This is expected as this study investigated younger people. Among the participants with SCI, one third were classified in the highest risk score group based on the plaque score and 6% of the controls.[115] This contrast the findings in this thesis where no effect sizes were in favor of an increased atherosclerotic burden among the participants with SCI. This may be due to that smoking was more frequent in the participants with SCI (42% vs 29%), in combination with the exclusion criterion of diabetes in the control group in that study.[115]

IMT is a surrogate marker for atherosclerosis as an increase in IMT predicts CVD and mortality.[187] Comparable studies show similar or increased IMT of the common

carotid artery between participants with SCI and controls.[116] No previous study reported IMT of the carotid bulb which has been shown to have a higher diagnostic accuracy as compared to measurements of common carotid artery alone.[188] Therefore, the significantly lower IMT of the carotid bulb among the participants compared with controls is noticeable and indicate a lower risk for CVD.

The lower IMT of the carotid bulb is in agreement with the effect sizes of the atherosclerosis results. Therefore, a hypothesis from this thesis is: if the atherosclerotic burden in fact is lower in people with cervical and upper thoracic SCI than controls (OR ranging from 0.38-0.54, significance levels 82-91%)?

The most likely explanation for the structural results is the lower cholesterol levels among the participants with SCI. This is based on the evidence of cholesterol exposure for the development of plaques.[171] The lower mean 24 hrs blood pressure may also be an important protective factor that contributes to the results.[3]

What is known?

Cardiovascular impairments have been reported in younger SCI populations with shorter time since injury. Overall, studies are scarce and not always comparing results with non-SCI controls.

Studies of cervical and upper thoracic SCI report:

- Reduced cardiovagal response in the subacute phase
- Reduced SDNN (sympathetic and parasympathetic activity) but not RMSSD (parasympathetic activity)
- Lower mean 24 hrs blood pressure
- Increased blood pressure variability
- Frequent nocturnal blood pressure rise
- Frequent orthostatic hypotension
- Greater occurrence of coronary artery calcium
- Similar occurrence but worse plaque score of carotid atherosclerosis
- Similar or increased IMT of the common carotid artery

What is new?

Cardiovascular functional impairments are overall reproduced, whereas structural impairments are both unexpected and in contrast with the scarce literature (i.e., no increase in atherosclerosis).

These results are new:

- Reduced cardiovagal response in the long-term phase.
- The altered circadian pattern of sympatho-vagal balance, i.e., LF/HF increases during the night. This indicates reduced daytime sympathetic activity and reduced nocturnal parasympathetic activity, opposite to the general population.
- The relationship (worse with a more rostral NLI) between several DBT and 24 hrs HRV variables, and blood pressure variability.
- CCTA results demonstrate no increase in coronary atherosclerosis.
- IMT of the carotid bulb is lower and indicates a lower CVD risk.

Pulmonary function and structure

Four different assessments were used to provide a novel, broad and in-depth description of pulmonary function and structure demonstrating pronounced pulmonary impairments but no considerable differences in structural impairments compared to controls. Several functional impairments were worse in relation to a more rostral NLI.

Pulmonary function

Among the participants with SCI, compared to controls, the predicted VC, FEV_1, MEF_{50}, D_{LCO} and k_{CO} were reduced. Airway resistance was increased and a greater stiffness and/or inhomogeneity of the pulmonary system were demonstrated. Several pulmonary functional impairments were worse in relation to a more rostral NLI.

Spirometry has been performed in several studies of people with SCI,[43] whereas diffusing capacity[189] and IOS assessments[84,117,118] are scarce. Previous studies have been performed in younger populations with shorter time since injury and rarely comparing with controls.[43,84,117-135,189]

In the 60s (Stone and Keltz)[119] and 70s (Fugl-Meyer and Grimby),[120,121] the characteristics of the restrictive pulmonary dysfunction in SCI was established. The spirometry results in this thesis are overall in agreement with previous studies[119-135] corroborating the inverse relationship between predicted FVC and NLI. Nevertheless, comparison with matched controls was not the case in previous studies as predicted % are considered normal values. Therefore, the magnitudes of the differences between participants with SCI and controls are noticeable. The participants' results were predicted 65-70% and the controls' were 100-109%, respectively. This may indicate that the pulmonary function was relatively worse among the participants with SCI as compared to previous studies. The controls performed spirometry after salbutamol administration which may affect these results, but this effect is not expected to be considerable as very few of the controls had either asthma or COPD (n=4 and 0, respectively).

FEV_1/FVC has previously been demonstrated to be normal in people with SCI and not related to NLI.[121,122,126,131,132] Among the participants, an inverse relationship between also NLI and FEV_1/FVC was found and corroborated by the total airway resistance (R5) assessed with IOS. This may indicate that NLI-dependant airway obstruction in this middle-aged population has developed.

Diffusing capacity has been reported in 18 people with SCI of which five had tetraplegia (mean age 47 years).[189] The mean predicted D_{LCO} among these people was 70%, which is slightly higher than this thesis (64%).[189] No other results of the D_{LCO} were reported and these were not corrected for hemoglobin, nor compared with controls.[189] Another study with five participants (mean age 39 years) with inspiratory and expiratory neuromuscular weaknesses reported comparable results (D_{LCO} 58% and k_{CO} 86%, respectively, whereas six controls' results were 95% and 89%, respectively).[190] Therefore, compromised diffusion is indicated among the participants with SCI, which may be due to pulmonary factors (ventilation) or cardiovascular factors (perfusion), or both. Pulmonary factors include for example emphysema and inhomogeneously aerated alveoli due to paradoxical breathing.[136,191] Cardiovascular factors affect the perfusion or diffusion distance of the alveoli. This can in turn be due to cardiac functional impairments and hypoxia related to obstructive sleep apnea.[191,192] Consequently, the pathophysiological mechanisms of reduced diffusing capacity are uncertain and remain to be investigated.

IOS has been performed in three studies[84,117,118] of people with SCI. The objectives of these studies[84,117,118] were different, performed in younger study populations and mostly reporting airway resistance exclusively. One study[84] compared airway resistance with controls and reported increased R5 and R20 in twelve people with cervical SCI (mean age 43 years) compared with nine controls, whereas another study[118] reported similar R5 and R20 between ten people with cervical SCI (mean age 41 years) and 11 controls. An increase in airway resistance has also been demonstrated with body plethysmography.[84]

Overall, airway resistance results in this thesis are in agreement with the literature. The increase in airway resistance in tetraplegia has been attributed to a loss of sympathetic innervation to the lungs.[84] However, these results have never been reproduced and sympathetic innervation of the lungs is controversial.[82] Instead, other factors are likely to be more important contributors to the increase in airway resistance. The most important is lower FRC which results in a closure of small airways and collapse of alveoli which increase the airway resistance.[72,73] Another is the paradoxical breathing pattern[120] which may cause an inhomogeneity of the lungs which increase airway resistance due to turbulent flow.[73,74]

The magnitude of the differences between participants with SCI and controls is influenced by the salbutamol exposure among the controls and warrant caution, i.e., the controls' airway resistance is reduced, possibly mostly affecting R20, and therefore the magnitudes are overestimated and R5-R20 underestimated.[193]

Reactance assessments have not previously been performed in SCI and compared with controls. The participants with SCI exhibited significant differences in each reactance variable (X5, fres and AX).[4] These results indicate a greater stiffness of the pulmonary system (properties of both the lung tissue and the chest wall).[4] The results may also be interpreted as a greater inhomogeneity of the pulmonary system. Both these mechanisms are likely to occur in SCI. A decrease in lung compliance and chest wall compliance has been reported.[43] Inhomogeneous distribution of aerated alveoli due to paradoxical breathing indicate inhomogeneity of the pulmonary system as described above. Fugl-Meyer and Grimby stated in 1971 that the decreased lung compliance "may lead to increased work of breathing", hence the interpretation of the implications on the pulmonary system is not new.[121]

Pulmonary structure

Among the participants with SCI compared to controls, there were no considerable differences in the occurrence of pulmonary structural impairments. NLI was related to the occurrence of pulmonary structural impairments and age to the occurrence of linear scars of atelectasis.

There are no comparable previous assessments of pulmonary structure using detailed CT protocol in SCI. One previous study[137] (1993) used CT to assess atelectasis in 14 people with respiratory muscle impairments of which eight (one participant older than 47 years) were due to cervical SCI. Thus, the results in this thesis are new, except for that instance.

Structural impairments were expected to occur more frequently than in controls as people with cervical and upper thoracic SCI exhibit substantial pulmonary functional impairments and respiratory disease burden.[20,21,43] Structural impairments were common in both participants and controls which may be interpreted that aging has a greater impact than the SCI. On the contrary, NLI and structural impairments were related implying that SCI may still exert an effect on structural impairments.

The relationship between age and atelectasis may be important as this relationship was not seen in the controls. The elastic recoil of the aging lung is reduced which causes premature closure of peripheral airways.[194] Therefore, it can be speculated that this indicates that the aging-related loss of elastic recoil has a greater impact in SCI. This effect may have clinical implications as it is related to the increasing incidence of pneumonia due to risk for stagnation of secretions.[194] Our results are supported by the previous CT study,[137] where only the older participant (age 69 years) had microatelectasis.

Finally, the results showed that interstitial structural findings were rare among the participants with SCI and, therefore, that the long-term exposure to pulmonary dysfunction did not exert an effect on the lung parenchyma. This was expected as the restrictive pulmonary disease in SCI is due to the neuromuscular weakness.[85]

What is known?

The restrictive spirometry pattern in cervical and upper thoracic SCI was established in 60s and 70s and reproduced in younger SCI populations with shorter time since injury. Studies assessing diffusing capacity and IOS are scarce and not always comparing results with non-SCI controls.

Studies of cervical and upper thoracic SCI report:

- Restrictive spirometry pattern
- Reduced predicted D_{LCO}
- Increased airway resistance
- Reduced lung compliance and chest wall compliance

What is new?

Pulmonary function is multidimensionally impaired. Pulmonary structure is surprisingly not considerably different among participants with SCI compared to controls, except for age being related to linear scars of atelectasis.

These results are new:

- Reduced D_{LCO} and k_{CO}
- Reduced elastance (increased stiffness/inhomogeneity) of the pulmonary system
- Linear scars of atelectasis related to age
- No considerable increase in the presence of structural impairments
- No interstitial structural impairments
- FEV_1/FVC worse with a more rostral NLI
- Increased total airway resistance (R5) with a more rostral NLI
- Presence of structural impairments related to a more rostral NLI

Clinical perspective and avenues for research

Current cardiopulmonary clinical management

Long-term clinical management of cardiopulmonary health among people with SCI is essential to prevent complications and improve life expectancy. However, SCI-specific cardiovascular clinical guidelines are absent.[195] A guideline based on scarce literature, expert opinion and knowledge from the general population has been suggested but received critique due to inappropriately applying findings from the general population in the SCI context.[178,179]

The scientific knowledge base of respiratory management is limited already in the acute and subacute phase and is based on clinical experience and expert opinion.[88] The literature suggests addressing factors that have detrimental effects on respiration such as smoking, obesity and physical inactivity, highlights the more prevalent sleep disordered breathing, and the importance of secretion clearing techniques and vaccination to prevent pulmonary complications.[196] Respiratory muscle training can improve respiratory muscle strength but the benefits are not clear.[88,196]

Taken together, our knowledge of cardiopulmonary management in long-term SCI is very limited and relies largely on clinical experiences and opinions.

Clinical challenges in SCI

Adopting knowledge generated from the general population in SCI is complicated and there are several basic examples of thresholds, assessments and conclusions that have been shown or regarded to be inappropriate to apply in people with SCI.[157,178,197] One such simple example is anthropometry.[157,197] BMI cut-offs underestimate visceral adiposity due to the lower lean body mass after SCI, and, therefore, SCI-adjusted cut-offs are suggested but have not been validated.[157,197] WC is considered a more precise assessment of visceral adiposity than BMI. However, WC is also inaccurate in SCI as demonstrated in imaging studies.[197] A current clinical opinion suggest a WC threshold of 86.5 cm in people with SCI (102 cm in the general population).[158,197] This cutoff, though, is based on a male population, which is another clinical challenge in SCI.[20,84,100,115,116,122-124,126,128,170,173,176,177,197]

Consequently, the clinical utility of the assessments in this thesis are important to consider. IOS may be a better tool to identify pulmonary functional impairments as it is effortless as compared to spirometry.[117] Imaging techniques identifying structural impairments add discriminatory capacity in the general population as compared to traditional risk scores.[148] Therefore, these new techniques may be important in the future development of risk assessment in people with SCI.

Another important aspect is that cardiopulmonary health in people with SCI is often examined by health professionals not experienced in SCI. In this thesis, the medical record review and interviews revealed several such examples. The most striking being the case with myocardial infarction due to AD as the emergency unit and cardiology unit were clueless regarding the cause of the significant troponin release. Another simple example is the general practitioner's prescription of antihypertensive agents to a person assessed during an (non-symptomatic) AD event causing a potentially dangerous increase in hypotensive episodes. The person quitted the medication by herself.

This can also be discussed in view of the knowledge and attitudes towards SCI in health care. Today, a scientific introduction to SCI describing these as "devastating injuries", which was common earlier, is refrained from in the literature of physical medicine and rehabilitation.[198] Long-term data describe people with SCI as generally satisfied with their lives and with strong psychological resources.[199] Though, during the data collection nuances of prejudices could be observed as, for example, a radiology nurse asked me "from which nursery home does she come from"? Indeed, unmet health care needs of people with disabilities are a major concern, which is likely to influence the clinical outcome negative in this population.[200] Therefore, empowerment, knowledge and self-management is

important in rehabilitation and the life-long follow up of people with SCI, as well as access to SCI specialists, for example through a contact nurse.

Finally, signs and symptoms may be different in people with SCI which make diagnosis difficult. For example, sensory impairments as well as exposure to symptom-triggering events may impede traditional symptoms and signs of exertional angina pectoris.[201] Therefore, it is emphasized to be extra precautious and thorough in the diagnostic task, i.e., to use diagnostic tools such as ECG, biochemistry, and radiology, liberally.

Taken together, the implications of the clinical challenges in SCI are possibly a worse outcome.

Multiple functional impairments – an increased vulnerability irrespective of structural impairments?

The characteristics and cardiopulmonary functional impairments reported among the participants with SCI are expected overall. On the contrary, cardiopulmonary structural impairments were not expected to be similar or even better than the controls. Substantial focus in SCI has been on different risk factors but to a lesser extent on cardiopulmonary epidemiology and imaging of cardiopulmonary structure.[164] Therefore, the interpretation of these cross-sectional results from a clinical perspective is speculative.

Atherosclerosis was expected to be more common among the participants with SCI due to CVD data[114,115] and that nearly three quarters were classified as having a high CVD risk (based on data from the general population). The CVD risk, in the general population, has been demonstrated to be linearly related to the plaque-burden as it is related to a greater likelihood of a plaque rupture which, in turn, can result in vascular thrombosis and a CVD event.[202] Accordingly, there are three steps in the development of a CVD event: plaque development, rupture and vascular thrombosis. In this thesis, data do not suggest a greater plaque-burden. However, several functional impairments may predispose people with cervical and upper thoracic SCI to plaque ruptures, vascular thrombosis, and a worse outcome (illustrated and summarized in Figure 17). This emphasizes the need for early detection and prevention.[202]

CVD comprises other conditions than atherosclerotic diseases. Dysrhythmias in cervical and upper thoracic SCI may also explain an increased CVD risk and mortality.[50,52,203] In this SCI population 12% had atrial fibrillation and one participant had been diagnosed when AD during bowel routines triggered paroxysmal atrial fibrillation. This, in combination with the myocardial infarction due to AD, emphasizes the present risk of AD affecting both the coronary conduction system and circulation.

The most relevant pulmonary structural impairment in this thesis is the linear scars of atelectasis due to the relationship with pneumonia. It was present in 54% of the participants with SCI and 37% of the controls (OR=2.1; 95% CI: 0.83-5.4). This effect size indicates a more than doubled odds of having the structural impairment but does not reach statistical significance. Nevertheless, these findings in two middle-aged populations on the threshold to old age are noteworthy. Compared with controls, the capacity to resist pulmonary complications, like pneumonia, among middle-aged people with cervical and upper thoracic SCI is reduced in several ways implying a worse outcome (illustrated and summarized in Figure 18).

Finally, it is also important to consider that cardiopulmonary functional impairments implicate a reduced capacity to resist acute medical conditions in general. In such events, for example, urinary tract infections, the cardiopulmonary demand increases. In the SPICA cohort, there were seven (28%) participants who had been hospitalized in the last five years due to infections.

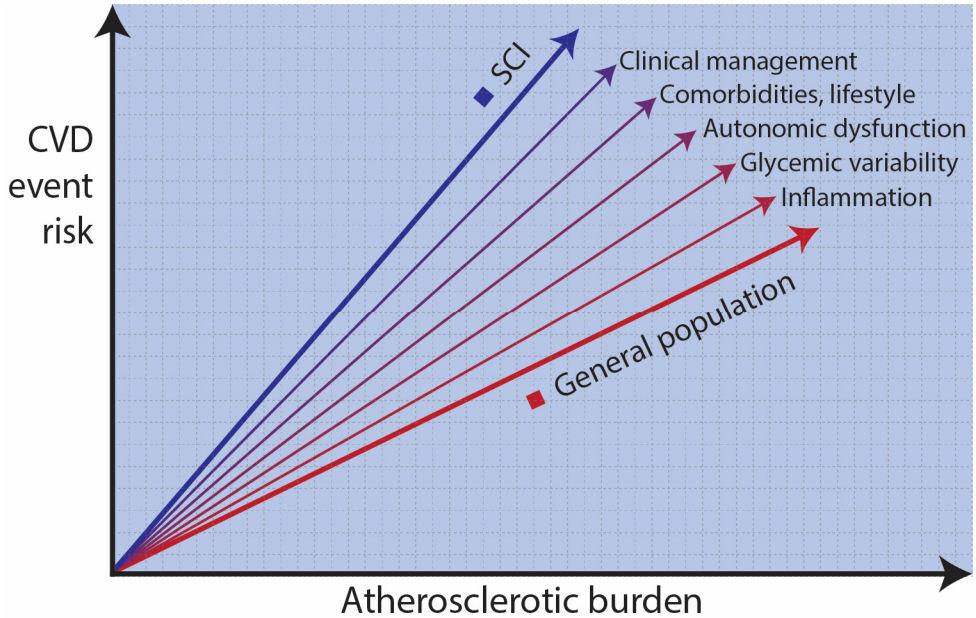


Figure 17. Factors hypothetically contributing to an increased vulnerability for CVD events among people with cervical and upper thoracic SCI compared to the general population

Inflammation is a key abnormality contributing to plaque development, plaque instability and thrombosis.[202] Glycemic variability associated with cardiovascular risk is indicated from the reverse J-shaped distribution of glucose levels.[175] Cardiovascular autonomic dysfunction may impact the circulation mechanically (blood pressure variability and autonomic dysreflexia),[204] have pro-inflammatory or direct pathophysiological effects on plaque formation.[147] Several comorbidities associated with CVD are highly prevalent (for example restrictive pulmonary disease,[87] obstructive sleep apnea[205] and atrial fibrillation[203]). Obstructive sleep apnea as an example may have pro-thrombotic effects.[205] Sedentary lifestyle may also influence the risk negatively.[64] Finally, the clinical challenges of diagnosis and attitudes from health care providers are likely to influence the outcome negatively.

CVD= cardiovascular disease

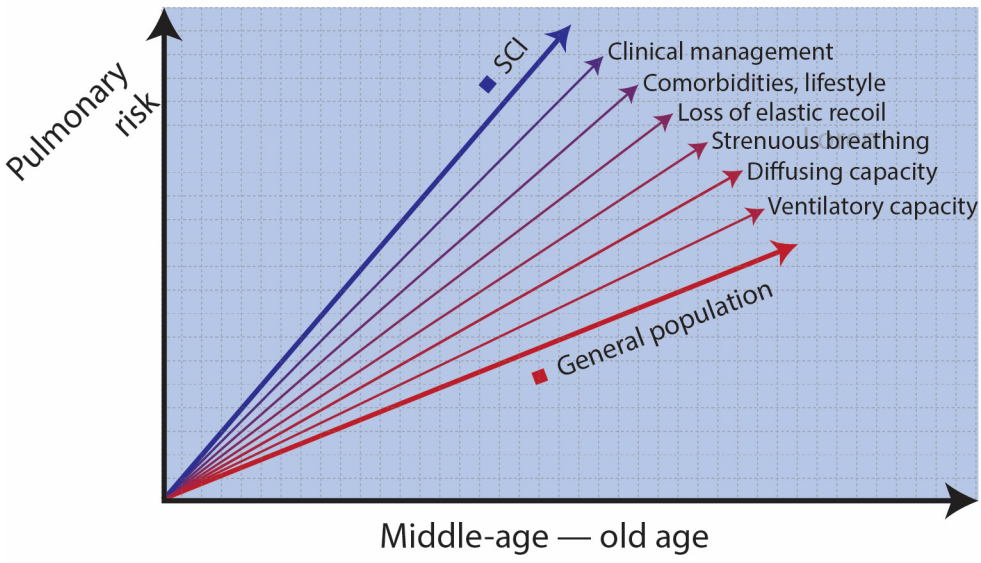


Figure 18. Factors hypothetically contributing to an increased vulnerability for pulmonary complications in the aging population with cervical and upper thoracic SCI compared to controls
Neuromuscular impairments cause reduced ventilatory capacity including coughing and managing secretions.[43] Reduced diffusion capacity impairs the gas exchange. The mechanical properties cause strenuous breathing due to increased airway resistance and stiffness of the pulmonary system. The relationship between linear scars of atelectasis and age may indicate loss of elastic recoil and susceptibility to pulmonary complications. Comorbidities and lifestyle, such as obesity further impair pulmonary function.[73] Finally, the clinical management may also have a negative impact due to attitudes and inexperienced health care providers. Altogether these factors indicate an increased vulnerability and a worse outcome of pulmonary complications in people with cervical and upper thoracic SCI.

In summary, the clinical picture revealed from this thesis describe a potentially vulnerable population where multiple functional impairments in combination with specific clinical challenges are likely to impact the clinical outcome negatively. The overall favorable description of cardiopulmonary structure is therefore important and promising. The long-term exposure to functional impairments in this cross-sectional thesis did not reveal considerable development of atherosclerosis and pulmonary structural impairments compared to controls. Future research efforts are paramount to understand the clinical relevance of the results in this thesis.

Cardiopulmonary prevention

This thesis was conducted in a small subpopulation of people with SCI. Larger and longitudinal studies are needed to confirm the results and to reveal the clinical significance. Studies of people with NLI below T6 and AIS D are needed to describe the whole traumatic-SCI population. It is also of importance that future studies are conducted longitudinally. One such opportunity is to use health data registers to prospectively follow up detailed cardiopulmonary data. Given the low prevalence of SCI, a multicentre approach to SCI research is emphasized.

Epidemiology

Epidemiology was not within the aim of this thesis, yet it is important to highlight that detailed cardiopulmonary epidemiology in SCI is scarce and is getting outdated. One example of a parameter that may be important is that the CVD risk factor kidney failure is likely to be less common today as hazardous bladder-emptying routines have been largely abandoned.[165,206] Thus, comparing results in this thesis with nearly 30-year-old data is complicated.[20] Longitudinal detailed data on morbidity and mortality of cardiopulmonary diseases in large population-based samples of people with long-term SCI are needed.

Future avenues in cardiopulmonary prevention

Beyond further understanding cardiopulmonary impairments and their clinical relevance, preventive measures of cardiopulmonary morbidity and mortality are warranted. The most important question in the future is whether these potentially modifiable factors are important and possible to target in order to improve the cardiopulmonary outcome? Here, some examples for future research are suggested.

CVD risk assessment needs to be further developed in SCI and preferentially not by using surrogate markers. In this thesis, the distribution of atherosclerosis among the participants with SCI were mostly among people with strong risk factors (smoking and diabetes; n=6) and it was substantial, causing mean coronary artery calcium score to be greater in participants than controls, despite a lower occurrence. Developing CVD risk assessments requires considerable research efforts but is regarded as a top priority to identify people with a heightened risk. Consequently, smokers and people with diabetes may be among the most important people to target as the clinical utility of imaging in SCI is further examined.

Regular physical activity has been demonstrated to improve cardiometabolic factors in people with SCI and international guidelines specifying type and dose of exercise have been established.[207] In the general population, positive health effects of cardiorespiratory fitness are widely accepted based on reductions in morbidity and mortality of cardiopulmonary diseases.[208] Evaluating these effects of physical activity, and not surrogate markers, in people with SCI would add scientific validity.

Statin use in people with SCI has been reported in a retrospective study to be related to reduced mortality.[209] The mechanism of action of statin is not purely to reduce cholesterol levels, it also leads to stabilization and regression of plaques.[210] The results in this thesis indicate that factors that may predispose people with SCI to plaque rupture are prevalent. Therefore, stabilization of plaques may have potential benefits. A randomized controlled trial could elucidate if there is a beneficial effect of statin use in SCI. Imaging of plaques could further aid that evaluation.

Similarly, calcium channel blockers have been reported to have the potential to prevent CVD due to effects on blood pressure variability in the general population.[211] Potential beneficial effect and tolerance in people with SCI could be answered in a randomized controlled trial. ABPM could further aid in the evaluation of the therapy.

The presence of pulmonary structural impairments was assessed but not quantified. Therefore, it may be that a quantification of the structural impairments would have yielded different results. Furthermore, an important hypothesis in future studies is whether people with cervical and upper thoracic SCI have a greater presence of atelectasis than controls (OR=2.1, significance level 88%)?

Which approach is the best to manage secretions in people with long-term SCI?[212] In this thesis only five participants had a cough assist device, but none used it on a regular basis. Based on the occurrence of severe pneumonia in this population, that may be reasonable. In this thesis, atelectasis was related to age among the participants with SCI and was present in all but one participant older than 60 years (89%). Different secretion management techniques could be evaluated in a crossover trial to evaluate the effect on pulmonary complications and pneumonia. This thesis suggests that people over 60 years should be targeted in such a study. Imaging atelectasis could further aid in the evaluation of the techniques.

Methodological considerations

Study design

The cross-sectional design was suitable to provide data on several variables of cardiopulmonary relevance to generate hypotheses for future research. Comparison with carefully matched controls from the general population enabled a detailed understanding of cardiopulmonary health among the participants with SCI. Another major strength of the studies comprising this thesis is the comprehensiveness of the assessments used to obtain both broad and in-depth data. No causal relationships could, however, be investigated, as the data collected are cross-sectional.

Study population and controls

The study population was population-based and included women, which is not always the case in SCI research.[20,84,100,115,116,122-124,126,128,170,173,176,177,197] The long history of SCI care at Skåne University Hospital in Lund, Sweden ensured that inclusion was population-based. Also, the response rate was good. I was responsible for the recruitment of participants and was in contact with most of the non-participants. A few of these declined due to health issues, whereas others declined due to work responsibilities, indicating good health. Thus, non-participants did not seem to have worse health than the participants. Dropout analyses demonstrated that the sample was representative for the whole population regarding gender, age, and injury characteristics.

Injury characteristics of the participants are expected from SCI epidemiology with a gender ratio in favour of men and cervical NLI being more common than upper thoracic NLI.[18,27] The inclusion criteria time since injury more than five years resulted in a considerable variety of the "exposure" to SCI in the study population (range from 6-53 years). This should be taken into consideration when interpreting the results as this variation makes the study population less uniform.

The inclusion criteria have strengths as well as limitations. The age range was determined by the SCAPIS' study protocol to enable the matching of controls.[3] The rationale in SCAPIS was to assess middle-aged people from the general population at risk for future compromises in cardiopulmonary health at baseline and then follow-up prospectively to identify risk factors.[3] The cross-sectional description of cardiopulmonary health of this study population may have been addressed at the "wrong" age. However, the exclusion of people of old age is likely to reduce survival bias and the exclusion of younger people, who are less likely to have developed for example atherosclerosis, is considered reasonable and therefore supports a fair timing.

Some injury characteristics were inclusion criteria due to the ambition to create a uniform sample of people with the lowest life expectancy (though excluding the very specific small population of people who are ventilator dependent with the lowest life expectancy). This is considered a strength but means that the results are not representative for people with non-traumatic SCI, NLI below T6, who are ventilator dependant or have AIS D. Moreover, data collected in NLI below T6 could have been used as controls as well, due to intact cardiopulmonary sympathetic innervation, which is likely to yield interesting results.

Ultimately, the inclusion criteria resulted in a small sample size, which is a major limitation of this thesis as the low statistical power limited the potential to draw more detailed inferences.

The matched controls from the general population have been shown to be representative of the target population of SCAPIS which is another strength.[213]

Other matching techniques, for example propensity matching, would have led to different control group characteristics, which is likely to have yielded different results.[214] The comparison between population-based samples matched on gender and age is in line with the aim of the study. This is rare in SCI research where convenient sampling of both cases and controls occur frequently. The control groups are therefore considered superior to comparable studies. This also enabled for sound statistical methods as comparisons generally could be performed using conditional logistic regression analyses.

Data collection

The data collection is a major strength of this thesis. I participated in all the data collection of the participants in SPICA and thereby had control over the data collection procedures. For both participants and controls, data were collected at the SCAPIS study site in Malmö during the same time period, by the same staff, using the same equipment. Further analyses were conducted by few investigators to avoid inter-rater bias. The collaboration with SCAPIS state-of-the-art baseline data collection thereby provided a high-class data collection of SPICA minimizing bias.

Despite the quality of the data collection there are some limitations. The SPICA data collection had to adhere to the SCAPIS baseline protocol.[3] This meant that cardiopulmonary variables relevant to SCI were not necessarily included as the aim of SCAPIS is to assess CVD and COPD in the general population. Another example of this limitation is the use of salbutamol among the controls before spirometry and IOS assessments due to the COPD study aim in SCAPIS. The last limitation is that the data collection of the participants in SPICA was carried out during the last months of the five-year long data collection. Completion of missing data could therefore not be done afterwards. Therefore, for example substantial CCTA data were missing.

Finally, the utility of some assessments in people with SCI has not been examined which may generate confounding. For example, results of the HRV assessments may be influenced by pulmonary factors.[12] Medications also influence the results. One important example is the frequent use of medications with anticholinergic effects among the participants with SCI.

Conclusions

This thesis has provided new knowledge of cardiopulmonary health in people with cervical and upper thoracic SCI many years after injury. This knowledge can be used to direct future research and to emphasize clinical issues in this population.

- Cardiopulmonary comorbidities and characteristics of the SPICA cohort are not standing out in relation to previous SCI research indicating representativeness.
- Cardiovascular risk factors are very common, classifying nearly three quarters of the participants in SPICA as having a high CVD risk.
- Self-reported exertional angina pectoris and pulmonary symptoms are rare, whereas cardiovascular autonomic dysfunction occur in most of the participants.
- The estimated risk for a CVD event, according to SCORE, is lower than the general population due to lower cholesterol levels. This indicates a significant protective factor in this population despite the high occurrence of CVD risk factors.
- Cardiopulmonary functions are overall impaired as compared to the general population and worse with a more rostral NLI. This implicates an increased vulnerability for cardiopulmonary complications which is greater in a more rostral NLI.
- The presence of cardiopulmonary structural impairments is not considerably different than in the general population.
- Age-related presence of linear scars of atelectasis in this population may indicate loss of elastic recoil and a specific vulnerability for pulmonary complications.
- Summarizing cardiopulmonary comorbidities and characteristics in combination with cardiopulmonary impairments reveal several factors implicating an increased vulnerability for cardiopulmonary complications irrespective of structural impairments.

Clinical implications

In this section, clinical considerations from this thesis are provided.

- The complexity of the impairments shown in this thesis demonstrates the need for a team specialized in SCI to manage these from a holistic perspective in the life-long follow-up program.
- Risk factors for CVD are highly prevalent, which emphasize the need for preventive strategies, such as physical activity, to be implemented in the follow-up routines.
- Sleep disorders are highly prevalent warranting evaluation of sleep quality in the follow-up.
- Management of cardiovascular autonomic dysfunction is of critical importance. The use of 24 hrs ECG and ABPM assessments, in combination with a diary to document for example bowel routines and transfers, can aid physicians to understand the mechanisms of blood pressure variability in people with SCI and thereby to elucidate treatment strategies.
- Current best practice of the management of pulmonary functional impairments are emphasized, such as to evaluate current strategies for managing the clearance of secretions from the lungs.
- Diffusing capacity and IOS can be useful in the future clinical evaluation of pulmonary function in people with SCI. These assessments have advantages over spirometry as they are effortless.
- The advanced imaging techniques of atherosclerosis used in the studies are considered feasible and may be useful in future CVD risk assessment in people with SCI.

Future perspectives

Overall, the results of this thesis need to be confirmed in other populations of SCI. The longitudinal impact of cardiopulmonary impairments on morbidity and mortality needs to be revealed.

Specific research questions generated from this thesis are:

- What is the current epidemiology of cardiopulmonary diseases in terms of morbidity and mortality?
- What are the pathophysiological mechanisms of reduced HRV in people with cervical and upper thoracic SCI?
- What are the pathophysiological mechanisms of altered circadian pattern of HRV and blood pressure in people with cervical and upper thoracic SCI?
- What is the prognostic significance of cardiovascular autonomic impairments, including altered circadian patterns, in people with cervical and upper thoracic SCI?
- What are the pathophysiological mechanisms of lower diffusing capacity in people with cervical and upper thoracic SCI?
- What is the prognostic significance of different pulmonary functional impairments in people with cervical and upper thoracic SCI?
- Does people with cervical and upper thoracic SCI have reduced LF_{day} indicating reduced sympathetic activity, and HF_{night} power indicating reduced parasympathetic activity than the general population?
- Does people with cervical and upper thoracic SCI have a lower atherosclerotic burden and a greater occurrence of atelectasis than the general population?
- If pulmonary structural impairments are further quantified, is there still no significant differences in people with cervical and upper thoracic SCI than controls?
- Are different preventive strategies effective in reducing cardiopulmonary morbidity and mortality beyond improving surrogate markers?

Populärvetenskaplig sammanfattning

I Sverige finns omkring 6 000 personer som lever med en ryggmärgsskada och årligen drabbas omkring 300 personer. Ungefär hälften av ryggmärgsskadorna är orsakade av olyckor medan resten är orsakade av sjukdomar såsom tumörer.

Idag lever personer som har drabbats av en ryggmärgsskada betydligt längre än tidigare tack vare förbättringar i vården för personer med ryggmärgsskada. Detta har lett till att det finns en grupp personer som har levt många decennier med en ryggmärgsskada, men där kunskaperna om deras hälsa är begränsad. Det som är känt är att livslängden inte är lika lång som för den övriga befolkningen, och att det framför allt är sjukdomar som drabbar hjärta, kärl och lungor som är orsaken till den kortare livslängden.

Ryggmärgen är en del av centrala nervsystemet och finns innesluten och skyddad inuti ryggraden. Ryggmärgen innehåller nerver som förmedlar information mellan hjärnan och kroppen. Till exempel går information ut i kroppen för att styra våra muskler så att vi kan gå, men också för att styra saker som vi inte alltid tänker på, såsom pulsen och blodtrycket. De senare funktionerna kallas autonoma funktioner, till skillnad från viljemässiga funktioner såsom att styra våra muskler.

Hjärtat, de stora blodkärlen och lungorna är exempel på organ som påverkas vid en ryggmärgsskada. Nerverna som går ut i kroppen till dessa organ lämnar ryggmärgen i nacken och övre delen av bröstryggen och påverkan blir därför mer uttalad om skadan är i den övre delen av ryggmärgen.

Syftet med den här avhandlingen var att på ett detaljerat sätt undersöka och beskriva hjärt-lunghälsan hos personer i medelåldern som har levt länge med en ryggmärgsskada i övre ryggmärgen orsakad av olycka. Därtill så jämfördes hjärt-lunghälsan hos deltagarna med ryggmärgsskada med personer från den övriga befolkningen för att se om det fanns några skillnader mellan personer med ryggmärgsskada och personer som inte har en ryggmärgsskada.

Målet med forskningsprojektet var att identifiera faktorer som kan ha betydelse för hjärt-lunghälsan för att inrikta framtida forskning på dessa faktorer. Genom fortsatt forskning kan vården utvecklas och förbättras för personer med ryggmärgsskada och förlänga livslängden. Vidare, genom att göra en noggrann kartläggning av hjärt-lunghälsan hos deltagarna, skapas en förståelse för aktuella vårdbehov i den här gruppen som direkt kan användas för att stärka hjärt-lunghälsan i denna grupp.

Avhandlingen visade att förekomsten av riskfaktorer för hjärt-kärlsjukdom var hög, till exempel övervikt. Däremot hade personerna med ryggmärgsskada lägre kolesterolvärden än den övriga befolkningen, vilket medförde att risken för hjärt-kärlsjukdom sammantaget var lägre för personerna med ryggmärgsskada. Detta bekräftades vid undersökning av blodkärlen där det framkom att förekomsten av åderförkalkning (som orsakar hjärtinfarkt och stroke) hos personer med ryggmärgsskada inte var ökad, vilket var motsatt till vad som var väntat.

När hjärtats och blodkärlens funktioner undersöktes framkom att dessa var påverkade jämfört med personer som inte har en ryggmärgsskada. Det skulle också kunna bidra till en ökad risk för hjärt-kärlsjukdom. Det är ett exempel på en viktig ny forskningsfråga som avhandlingen har skapat. Bidrar den nedsatta hjärt-kärlfunktionen till en ökad risk för att drabbas av hjärt-kärlsjukdom såsom hjärtinfarkt? Vilka av dessa faktorer är då viktiga och hur kan de förebyggas?

Avhandlingen kunde också visa att lungfunktionen var sämre hos personerna med ryggmärgsskada vilket exempelvis gör att förmågan att hosta är lägre. Det bidrar sannolikt till en högre sårbarhet för sjukdomar i lungorna såsom lunginflammation. I befolkningen generellt ökar förekomsten av lunginflammation kraftigt efter medelåldern varför avhandlingen visar på att det är viktigt att på olika sätt förebygga lunginflammation för personer med ryggmärgsskada. Detta kan vara allt från att vaccinera sig för Covid-19 till att ha olika strategier för att få en bra hoststöt. Även här behövs mer forskning för att förstå vilken betydelse de olika faktorerna som orsakar nedsatt lungfunktion har för lungsjukdomar på sikt och hur man kan behandla dessa.

Sammantaget kunde avhandlingen visa på tydliga skillnader i hjärtats, kärlens och lungornas funktion men däremot inte att vävnaden i dessa organ hade påverkats med till exempel mycket åderförkalkning. Det är sannolikt att den försämrade hjärt-lunghälsan gör personer med ryggmärgsskada i övre delen av ryggmärgen mer sårbara för sjukdomar som uppstår i samband med åldrandet såsom lunginflammation. Det kan också innebära att det är större risk att en person med ryggmärgsskada drabbas av en hjärtinfarkt trots en lägre omfattning av åderförkalkning jämfört med personer som inte har en ryggmärgsskada. Följaktligen behöver den fortsatta forskningen inriktas på att förstå vilken betydelse dessa faktorer har för att utveckla sjukdomar i hjärta och lungor. Detta för att i sin tur kunna påverka dessa faktorer och öka hjärt-lunghälsan och därmed livslängden.

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😊

References

1. Hubli M, Gee CM, Krassioukov AV: Refined assessment of blood pressure instability after spinal cord injury. Am J Hypertens. 2015;28:173–181.
2. Kirshblum SC, Waring W, Biering-Sørensen F, et al: Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. J Spinal Cord Med. 2011;34:547–554.
3. Bergstrom G, Berglund G, Blomberg A, et al: The Swedish CArdioPulmonary BioImage Study: objectives and design. J Intern Med. 2015;278:645–659.
4. King GG, Bates J, Berger KI, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020;55:1900753.
5. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. Radiology. 2008;246:697–722.
6. McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD, Kalender WA. Coronary artery calcium: a multi-institutional, multimanufacturer international standard for quantification at cardiac CT. Radiology. 2007;243:527–538.
7. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. 2007;50:1161–1170.
8. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281–1357.
9. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–735.
10. Löllgen D, Müeck-Weymann M, Beise RD. The deep breathing test: median-based expiration-inspiration difference is the measure of choice. Muscle Nerve. 2009;39:536–544.
11. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(Suppl 16):5–40.
12. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017;5:258.

13. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34:290–296.
14. National Library of Medicine, Medical Subject Headings [Accessed 2023 October 2]. https://meshb.nlm.nih.gov/record/ui?ui=D008875
15. Chamberlain JD, Meier S, Mader L, von Groote PM, Brinkhof MW. Mortality and longevity after a spinal cord injury: systematic review and meta-analysis. Neuroepidemiology. 2015;44:182–198.
16. Guttmann L. New hope for spinal cord sufferers. Paraplegia. 1979;17:6–15.
17. Mesard L, Carmody A, Mannarino E, Ruge D. Survival after spinal cord trauma. A life table analysis. Arch Neurol. 1978;35:78–83.
18. Devivo MJ: Epidemiology of traumatic spinal cord injury: trends and future implications.Spinal Cord 2012;50:365–372.
19. Jörgensen S, Iwarsson S, Norin L, Lexell J. The Swedish Aging With Spinal Cord Injury Study (SASCIS): methodology and initial results. PM R. 2016;8:667–677.
20. Garshick E, Kelley A, Cohen SA, et al. A prospective assessment of mortality in chronic spinal cord injury. Spinal Cord. 2005;43:408–416.
21. DeVivo MJ, Chen Y, Wen H. Cause of Death Trends Among Persons With Spinal Cord Injury in the United States: 1960-2017. Arch Phys Med Rehabil. 2022;103:634–641.
22. Hultborn H. Spinal reflexes, mechanisms and concepts: from Eccles to Lundberg and beyond. Prog Neurobiol. 2006;78:215–232.
23. Jänig W. Spinal cord reflex organization of sympathetic systems. Prog Brain Res. 1996;107:43–77.
24. Wecht JM, Krassioukov AV, Alexander M, et al. International Standards to document Autonomic Function following SCI (ISAFSCI): Second Edition. Top Spinal Cord Inj Rehabil. 2021;27:23–49.
25. Barbiellini Amidei C, Salmaso L, Bellio S, Saia M. Epidemiology of traumatic spinal cord injury: a large population-based study. Spinal Cord. 2022;60:812–819.
26. New PW, Marshall R. International Spinal Cord Injury Data Sets for non-traumatic spinal cord injury. Spinal Cord. 2014;52:123–132.
27. Svenskt Register för Rehabiliteringsmedicin. Årsrapport WebRehab Sweden 2018, ryggmärgsskadevariabler [Accessed 2023 October 3] https://svereh.registercentrum.se/download?fileUrl=https://registercentrum.blob.core.windows.net/svereh/r/Arsrapport-WebRehab-Sweden-2018-ryggmargsskadevariabler-BJxHB5oXZF.pdf
28. van den Berg ME, Castellote JM, de Pedro-Cuesta J, Mahillo-Fernandez I. Survival after spinal cord injury: a systematic review. J Neurotrauma. 2010;27:1517–1528.

29. Middleton JW, Dayton A, Walsh J, Rutkowski SB, Leong G, Duong S. Life expectancy after spinal cord injury: a 50-year study. Spinal Cord. 2012;50:803–811.
30. World Health Organization, Global Health Estimates: Life expectancy and leading causes of death and disability. [Accessed 2023 October 3] https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-life-expectancy-and-healthy-life-expectancy
31. International Spinal Cord Society. International perspectives on spinal cord injury. Bickenbach J, editor. Geneva: World Health Organization; 2013.
32. Lexell J, Brogårdh C. The use of ICF in the neurorehabilitation process. NeuroRehabilitation. 2015;36:5–9.
33. World Health Organization. The International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization; 2001.
34. World Health Organization & World Bank. World report on disability (2011). [Accessed 2023 October 3] http://www.who.int/disabilities/world_report/2011/en/
35. Hasnan N, Patrick Engkasan J, Ramakrishnan K, et al. Follow-up after spinal cord injury. In: Chhabra HS, editor. ISCoS Textbook on comprehensive management of spinal cord injuries. Haryana, India: Lippincott Williams & Wilkins; 2015. p. 888–905.
36. Jensen MP, Molton IR, Groah SL, et al. Secondary health conditions in individuals aging with SCI: terminology, concepts and analytic approaches. Spinal Cord. 2012;50:373–378.
37. Jeong SJ, Cho SY, Oh SJ . Spinal cord/brain injury and the neurogenic bladder. Urol Clin North Am. 2010;37:537–546.
38. Valles M, Vidal J, Clave P, Mearin F. Bowel dysfunction in patients with motor complete spinal cord injury: clinical, neurological, and pathophysiological associations. Am J Gastroenterol. 2006;101:2290–2299.
39. Jensen MP, Hoffman AJ, Cardenas DD. Chronic pain in individuals with spinal cord injury: a survey and longitudinal study. Spinal Cord. 2005;43:704–712.
40. Adams MM, Hicks AL. Spasticity after spinal cord injury. Spinal Cord 2005;43:577–586.
41. Jiang SD, Dai LY, Jiang LS. Osteoporosis after spinal cord injury. Osteoporos Int. 2006;17:180–192.
42. Phillips AA, Krassioukov AV: Contemporary cardiovascular concerns after spinal cord injury: mechanisms, maladaptations, and management. J Neurotrauma. 2015;32:1927–1942.
43. Schilero GJ, Radulovic M, Wecht JM, et al: A center's experience: pulmonary function in spinal cord injury. Lung. 2014;192:339–346.
44. Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology. 2014;83:261–271.
45. Krassioukov A. Autonomic function following cervical spinal cord injury. Respir Physiol Neurobiol. 2009;169:157–164.
46. Mangoni ME, Nargeot J. Genesis and regulation of the heart automaticity. Physiol Rev. 2008;88:919–982.

47. Fink GD. Arthur C. Corcoran Memorial Lecture. Sympathetic activity, vascular capacitance, and long-term regulation of arterial pressure. Hypertension. 2009;53:307–312.
48. Guyton AC, Coleman TG, Granger HJ. Circulation: overall regulation. Annu Rev Physiol. 1972;34:13–46.
49. Guyton AC. Kidneys and fluids in pressure regulation. Small volume but large pressure changes. Hypertension. 1992;19:I2–8.
50. Biering-Sørensen F, Biering-Sørensen T, Liu N, Malmqvist L, Wecht JM, Krassioukov A. Alterations in cardiac autonomic control in spinal cord injury. Auton Neurosci. 2018;209:4–18.
51. Claydon VE, Steeves JD, Krassioukov A. Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology. Spinal Cord. 2006;44:341–351.
52. Dolinak D, Balraj E. Autonomic dysreflexia and sudden death in people with traumatic spinal cord injury. Am J Forensic Med Pathol. 2007;28:95–98.
53. Krassioukov A, Warburton DE, Teasell R, Eng JJ. Spinal Cord Injury Rehabilitation Evidence Research Team. A systematic review of the management of autonomic dysreflexia after spinal cord injury. Arch Phys Med Rehabil. 2009;90:682–695.
54. Karlsson AK. Autonomic dysreflexia. Spinal Cord. 1999;37:383–391.
55. Wang S, Wecht JM, Ugiliweneza B, Legg Ditterline B. Increased Prevalence of Blood Pressure Instability Over Twenty-Four Hours in Chronic Spinal Cord Injury. Neurotrauma Rep. 2022;3:522–533.
56. National Library of Medicine, Medical Subject Headings [Accessed 2023 October 4]. https://www.ncbi.nlm.nih.gov/mesh/68002318
57. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Med. 2013;11:117.
58. Groah SL, Weitzenkamp D, Sett P, Soni B, Savic G. The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. Spinal Cord. 2001;39:310–317.
59. Zambach C, Fedorowski A, Gerward S, Johansson M, Engström G, Hamrefors V. Subclinical atherosclerosis and risk factors in relation to autonomic indices in the general population. J Hypertens. 2023;41:759–767.
60. Saunders LL, Clarke A, Tate DG, et al: Lifetime prevalence of chronic health conditions among persons with spinal cord injury. Arch Phys Med Rehabil. 2015;96:673–679.
61. Gater DR Jr, Farkas GJ, Tiozzo E. Pathophysiology of Neurogenic Obesity After Spinal Cord Injury. Top Spinal Cord Inj Rehabil. 2021;27:1–10.
62. Gilbert O, Croffoot JR, Taylor AJ, Nash M, Schomer K, Groah S. Serum lipid concentrations among persons with spinal cord injury - a systematic review and metaanalysis of the literature. Atherosclerosis. 2014;232:305–312.
63. Elmelund M, Oturai PS, Toson B, et al: Forty-five-year follow-up on the renal function after spinal cord injury. Spinal Cord. 2016;54:445–451.

64. Jörgensen S, Martin Ginis KA, Lexell J: Leisure time physical activity among older adults with long-term spinal cord injury. Spinal Cord. 2017;55:848–856.
65. West JB. A lifetime of pulmonary gas exchange. Physiol Rep. 2018;6:e13903.
66. Wagner PD. The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. Eur Respir J. 2015;45:227–243.
67. Aliverti A. The respiratory muscles during exercise. Breathe (Sheff). 2016;12:165–168.
68. Perlman CE. The Contribution of Surface Tension-Dependent Alveolar Septal Stress Concentrations to Ventilation-Induced Lung Injury in the Acute Respiratory Distress Syndrome. Front Physiol. 2020;11:388.
69. Haagsman HP, van Golde LM. Synthesis and assembly of lung surfactant. Annu Rev Physiol. 1991;53:441–464.
70. Bhana RH, Magan AB. Lung Mechanics: A Review of Solid Mechanical Elasticity in Lung Parenchyma. J Elast. 2023;153:53–117.
71. Gibson GJ. Lung volumes and elasticity. Clin Chest Med. 2001;22:623–635.
72. Bates JH. Systems physiology of the airways in health and obstructive pulmonary disease. Wiley Interdiscip Rev Syst Biol Med. 2016;8:423–437.
73. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol (1985). 2010;108:206–211.
74. Mann LM, Granger EA, Chan JS, Yu A, Molgat-Seon Y, Dominelli PB. Minimizing airflow turbulence in women lowers the work of breathing to levels similar to men. J Appl Physiol (1985). 2020;129:410–418.
75. Carvalho AR, Zin WA. Respiratory system dynamical mechanical properties: modeling in time and frequency domain. Biophys Rev. 2011;3:71.
76. De Troyer A, Boriek AM. Mechanics of the respiratory muscles. Compr Physiol. 2011;1:1273–1300.
77. Sieck GC, Ferreira LF, Reid MB, Mantilla CB. Mechanical properties of respiratory muscles. Compr Physiol. 2013;3:1553–1567.
78. Ikeda K, Kawakami K, Onimaru H, et al. The respiratory control mechanisms in the brainstem and spinal cord: integrative views of the neuroanatomy and neurophysiology. J Physiol Sci. 2017;67:45–62.
79. Fisher JP, Zera T, Paton JFR. Respiratory-cardiovascular interactions. Handb Clin Neurol. 2022;188:279–308.
80. Sheehan DW, Farhi LE. Local pulmonary blood flow: control and gas exchange. Respir Physiol. 1993;94:91–107.
81. Vaillancourt M, Chia P, Sarji S, et al. Autonomic nervous system involvement in pulmonary arterial hypertension. Respir Res. 2017;18:201.
82. Belvisi MG. Overview of the innervation of the lung. Curr Opin Pharmacol. 2002;2:211–215.
83. van der Velden VH, Hulsmann AR. Autonomic innervation of human airways: structure, function, and pathophysiology in asthma. Neuroimmunomodulation. 1999;6:145–159.

84. Radulovic M, Schilero GJ, Wecht JM, et al. Airflow obstruction and reversibility in spinal cord injury: evidence for functional sympathetic innervation. Arch Phys Med Rehabil. 2008;89:2349–2353.
85. Wolfe LF, Joyce NC, McDonald CM, Benditt JO, Finder J. Management of pulmonary complications in neuromuscular disease. Phys Med Rehabil Clin N Am. 2012;23:829–853.
86. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J. 2022;60:2101499.
87. Guerra S, Sherrill DL, Venker C, et al. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. Thorax. 2010;65:499–504.
88. Galeiras Vázquez R, Rascado Sedes P, Mourelo Fariña M, Montoto Marqués A, Ferreiro Velasco ME. Respiratory management in the patient with spinal cord injury. Biomed Res Int. 2013;2013:168757.
89. Terson de Paleville DG, McKay WB, Folz RJ, Ovechkin AV. Respiratory motor control disrupted by spinal cord injury: mechanisms, evaluation, and restoration. Transl Stroke Res. 2011;2:463–473.
90. Dunnill MS. The anatomy of restrictive lung disease. Hum Pathol. 1970;1:265–274.
91. Adegeest CY, van Gent JAN, Stolwijk-Swüste JM, et al. Influence of severity and level of injury on the occurrence of complications during the subacute and chronic stage of traumatic spinal cord injury: a systematic review. J Neurosurg Spine. 2021;36:632–652.
92. Hitzig SL, Tonack M, Campbell KA, et al. Secondary health complications in an aging Canadian spinal cord injury sample. Am J Phys Med Rehabil. 2008;87:545–555.
93. McKinley WO, Jackson AB, Cardenas DD, DeVivo MJ. Long-term medical complications after traumatic spinal cord injury: a regional model systems analysis. Arch Phys Med Rehabil. 1999;80:1402–1410.
94. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis 2017;65:1806–1812.
95. Graco M, McDonald L, Green SE, Jackson ML, Berlowitz DJ. Prevalence of sleep-disordered breathing in people with tetraplegia-a systematic review and meta-analysis. Spinal Cord. 2021;59:474–484.
96. Salari N, Khazaie H, Abolfathi M, et al. The effect of obstructive sleep apnea on the increased risk of cardiovascular disease: a systematic review and meta-analysis. Neurol Sci. 2022;43:219–231.
97. Berger MJ, Kimpinski K, Currie KD, Nouraei H, Sadeghi M, Krassioukov AV. Multi-Domain Assessment of Autonomic Function in Spinal Cord Injury Using a Modified Autonomic Reflex Screen. J Neurotrauma. 2017;34:2624–2633.
98. Wang YH, Huang TS, Lin JL, et al. Decreased autonomic nervous system activity as assessed by heart rate variability in patients with chronic tetraplegia. Arch Phys Med Rehabil. 2000;81:1181–1184.

99. Rosado-Rivera D, Radulovic M, Handrakis JP, et al. Comparison of 24-hour cardiovascular and autonomic function in paraplegia, tetraplegia, and control groups: implications for cardiovascular risk. J Spinal Cord Med. 2011;34:395–403.
100. Bunten DC, Warner AL, Brunnemann SR, Segal JL. Heart rate variability is altered following spinal cord injury. Clin Auton Res. 1998;8:329–334.
101. Krstacić A, Krstacić G, Gamberger D. Control of heart rate by the autonomic nervous system in acute spinal cord injury. Acta Clin Croat. 2013;52:430–435.
102. Fang X, Goh MY, O'Callaghan C, Berlowitz D. Relationship between autonomic cardiovascular control and obstructive sleep apnoea in persons with spinal cord injury: a retrospective study. Spinal Cord Ser Cases. 2018;4:29.
103. Curt A, Nitsche B, Rodic B, Schurch B, Dietz V. Assessment of autonomic dysreflexia in patients with spinal cord injury. J Neurol Neurosurg Psychiatry. 1997;62:473–477.
104. Nitsche B, Perschak H, Curt A, Dietz V. Loss of circadian blood pressure variability in complete tetraplegia. J Hum Hypertens. 1996;10:311–317.
105. Thayer JF, Sollers JJ 3rd, Clamor A, Koenig J, Hagglund KJ. The association of resting state heart rate variability and 24-hour blood pressure variability in spinal cord injury. J Neurol Sci. 2016;361:52–59.
106. Goh MY, Millard MS, Wong EC, Brown DJ, Frauman AG, O'Callaghan CJ. Diurnal blood pressure and urine production in acute spinal cord injury compared with controls. Spinal Cord. 2017;55:39–46.
107. Popok DW, West CR, Hubli M, Currie KD, Krassioukov AV. Characterizing the Severity of Autonomic Cardiovascular Dysfunction after Spinal Cord Injury Using a Novel 24 Hour Ambulatory Blood Pressure Analysis Software. J Neurotrauma. 2017;34:559–566.
108. Krum H, Howes LG, Brown DJ, Louis WJ. Blood pressure variability in tetraplegic patients with autonomic hyperreflexia. Paraplegia. 1989;27:284–288.
109. Krum H, Louis WJ, Brown DJ, Jackman GP, Howes LG. Diurnal blood pressure variation in quadriplegic chronic spinal cord injury patients. Clin Sci (Lond). 1991;80:271–276.
110. Cívicos Sánchez N, Acera M, Murueta-Goyena A, et al. Quantitative analysis of dysautonomia in patients with autonomic dysreflexia. J Neurol. 2021;268:2985–2994.
111. Wang S, Wecht JM, Legg Ditterline B, et al. Heart rate and blood pressure response improve the prediction of orthostatic cardiovascular dysregulation in persons with chronic spinal cord injury. Physiol Rep. 2020;8:e14617.
112. Wecht JM, Weir JP, Galea M, Martinez S, Bauman WA. Prevalence of abnormal systemic hemodynamics in veterans with and without spinal cord injury. Arch Phys Med Rehabil. 2015;96:1071–1079.
113. Sahota IS, Ravensbergen HR, McGrath MS, Claydon VE. Cerebrovascular responses to orthostatic stress after spinal cord injury. J Neurotrauma. 2012;29:2446–2456.

114. Orakzai SH, Orakzai RH, Ahmadi N, et al. Measurement of coronary artery calcification by electron beam computerized tomography in persons with chronic spinal cord injury: evidence for increased atherosclerotic burden. Spinal Cord. 2007;45:775–779.
115. Wang YH, Chen SY, Wang TD, Hwang BS, Huang TS, Su TC. The relationships among serum glucose, albumin concentrations and carotid atherosclerosis in men with spinal cord injury. Atherosclerosis. 2009;206:528–534.
116. Hoskin JD, Miyatani M, Craven BC. Quality reporting of carotid intima-media thickness methodology; Current state of the science in the field of spinal cord injury. J Spinal Cord Med. 2018;41:479–489.
117. Cirnigliaro CM, Lesser M, Moyer J, Kirshblum SC, Bauman WA, Spungen AM. Reproducibility and effect of posture on impulse oscillation parameters in persons with spinal cord injury. J Spinal Cord Med. 2012;35:28–34.
118. Schilero GJ, Hobson JC, Singh K, Spungen AM, Bauman WA, Radulovic M. Bronchodilator effects of ipratropium bromide and albuterol sulfate among subjects with tetraplegia. J Spinal Cord Med. 2018;41:42–47.
119. Stone DJ, Keltz H. The effect of respiratory muscle dysfunction on pulmonary function: studies in patients with spinal cord injuries. Am Rev Respir Dis. 1963;88:621–629.
120. Fugl-Meyer AR. Effects of respiratory muscle paralysis in tetraplegic and paraplegic patients. Scand J Rehabil Med. 1971;3:141–150.
121. Fugl-Meyer AR, Grimby G. Ventilatory function in tetraplegic patients. Scand J Rehabil Med. 1971;3:151–160.
122. Pithon KR, Martins LE, Renno AC, Abreu DC, Cliquet A Jr. Pulmonary function testing in quadriplegic subjects. Spinal Cord. 2008;46:275–277.
123. Stolzmann KL, Gagnon DR, Brown R, Tun CG, Garshick E. Longitudinal change in FEV1 and FVC in chronic spinal cord injury. Am J Respir Crit Care Med. 2008;177:781–786.
124. Jain NB, Brown R, Tun CG, Gagnon D, Garshick E. Determinants of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC in chronic spinal cord injury. Arch Phys Med Rehabil. 2006;87:1327–1333.
125. Linn WS, Spungen AM, Gong H Jr, Adkins RH, Bauman WA, Waters RL. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. Spinal Cord. 2001;39:263–268.
126. Spungen AM, Dicpinigaitis PV, Almenoff PL, Bauman WA. Pulmonary obstruction in individuals with cervical spinal cord lesions unmasked by bronchodilator administration. Paraplegia. 1993;31:404–407.
127. Ohry A, Molho M, Rozin R. Alterations of pulmonary function in spinal cord injured patients. Paraplegia. 1975;13:101–108.
128. Almenoff PL, Spungen AM, Lesser M, Bauman WA. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. Lung. 1995;173:297–306.

129. Forner JV. Lung volumes and mechanics of breathing in tetraplegics. Paraplegia. 1980;18:258–266.
130. Bluechardt MH, Wiens M, Thomas SG, Plyley MJ. Repeated measurements of pulmonary function following spinal cord injury. Paraplegia. 1992;30:768–774.
131. Roth EJ, Nussbaum SB, Berkowitz M, et al. Pulmonary function testing in spinal cord injury: correlation with vital capacity. Paraplegia. 1995;33:454–457.
132. Anke A, Aksnes AK, Stanghelle JK, Hjeltnes N. Lung volumes in tetraplegic patients according to cervical spinal cord injury level. Scand J Rehabil Med. 1993;25:73–77.
133. Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. Am Rev Respir Dis. 1981;124:41–44.
134. Kokkola K, Moller K, Lehtonen T. Pulmonary function in tetraplegic and paraplegic patients. Ann Clin Res. 1975;7:76–79.
135. Fujiwara T, Hara Y, Chino N. Expiratory function in complete tetraplegics: study of spirometry, maximal expiratory pressure, and muscle activity of pectoralis major and latissimus dorsi muscles. Am J Phys Med Rehabil. 1999;78:464–469.
136. Hiraizumi Y, Fujimaki E, Hishida T, Maruyama T, Takeuchi M. Regional lung perfusion and ventilation with radioisotopes in cervical cord-injured patients. Clin Nucl Med. 1986;11:352–357.
137. Estenne M, Gevenois PA, Kinnear W, Soudon P, Heilporn A, De Troyer A. Lung volume restriction in patients with chronic respiratory muscle weakness: the role of microatelectasis. Thorax. 1993;48:698–701.
138. Strengthening the reporting of observational studies in epidemiology, STROBE Statement [Accessed 2023 Oct 5]. http://www.strobe-statement.org.
139. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–370.
140. Bohannon RW, Smith MB: Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67:206–207.
141. Antonovsky A: The structure and properties of the sense of coherence scale. Soc Sci Med. 1993;36:725–733.
142. Catz A, Itzkovich M, Agranov E, et al: SCIM—spinal cord independence measure: a new disability scale for patients with spinal cord lesions. Spinal Cord. 1997;35:850–856.
143. Adams MM, Ginis KA, Hicks AL: The spinal cord injury spasticity evaluation tool: development and evaluation. Arch Phys Med Rehabil. 2007;88:1185–1192.
144. Thomassen SA, Johannesen IL, Erlandsen EJ, et al: Serum cystatin C as a marker of the renal function in patients with spinal cord injury. Spinal Cord. 2002;40:524–528.
145. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003.
146. Wilhelmsen L,Wedel H, Conroy R, et al. The Swedish SCORE chart for cardiovascular risk. Better possibilities for prevention of cardiovascular diseases [in Swedish]. Läkartidningen. 2004;101:1798–1801.

147. Engström G, Hamrefors V, Fedorowski A, et al. Cardiovagal Function Measured by the Deep Breathing Test: Relationships With Coronary Atherosclerosis. J Am Heart Assoc. 2022;11:e024053.
148. Bergström G, Persson M, Adiels M, et al. Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population. Circulation. 2021;144:916–929.
149. Wikstrand J. Methodological considerations of ultrasound measurement of carotid artery intima-media thickness and lumen diameter. Clin Physiol Funct Imaging. 2007;27:341–345.
150. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J. 2005;26:153–161.
151. Kelley A, Garshick E, Gross ER, Lieberman SL, Tun CG, Brown R. Spirometry testing standards in spinal cord injury. Chest. 2003;123:725–730.
152. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J. 1993;6(Suppl 16):41–52.
153. Hennessy S, Bilker WB, Berlin JA, Strom BL. Factors influencing the optimal control-to-case ratio in matched case-control studies [published correction appears in Am J Epidemiol. 1999 Mar 1;149:489]. Am J Epidemiol. 1999;149:195–197.
154. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–2194.
155. The Swedish Parliament, Ethical Review Act (2003:460) [in Swedish], [Accessed 2023 Oct 5]. https://www.riksdagen.se/sv/dokument-och-lagar/dokument/svensk-forfattningssamling/lag-2003460-om-etikprovning-av-forskning-som_sfs-2003-460/
156. United Nations, Convention on the Rights of Persons with Disabilities (CRPD), [Accessed 2023 Oct 5]. https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities/convention-on-the-rights-of-persons-with-disabilities-2.html
157. Laughton GE, Buchholz AC, Martin Ginis KA, et al: Lowering body mass index cutoffs better identifies obese persons with spinal cord injury. Spinal Cord. 2009;47:757–762.
158. Flint AJ, Rexrode KM, Hu FB, et al: Body mass index, waist circumference, and risk of coronary heart disease: a prospective study among men and women. Obes Res Clin Pract. 2010;4:e171–181.
159. Nazare JA, Smith J, Borel AL, et al. Usefulness of measuring both body mass index and waist circumference for the estimation of visceral adiposity and related cardiometabolic risk profile (from the INSPIRE ME IAA study) [published correction appears in Am J Cardiol. 2015 May 1;115:1323]. Am J Cardiol. 2015;115:307–315.
160. Elagizi A, Kachur S, Carbone S, Lavie CJ, Blair SN. A Review of Obesity, Physical Activity, and Cardiovascular Disease. Curr Obes Rep. 2020;9:571–581.

161. Saunders LL, Krause JS, Saladin M, Carpenter MJ. Prevalence of cigarette smoking and attempts to quit in a population-based cohort with spinal cord injury. Spinal Cord. 2015;53:641–645.
162. Krause JS, Cao Y, Saunders LL. Changes in cigarette smoking after traumatic spinal cord injury. Rehabil Psychol. 2015;60:379–382.
163. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124:2145–2154.
164. Cragg JJ, Noonan VK, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury: results from a national population health survey. Neurology. 2013;81:723–728.
165. Go AS, Chertow GM, Fan D, et al: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–1305.
166. Lee ES, Joo MC. Prevalence of Autonomic Dysreflexia in Patients with Spinal Cord Injury above T6. Biomed Res Int. 2017;2017:2027594.
167. Ho CP, Krassioukov AV: Autonomic dysreflexia and myocardial ischemia. Spinal Cord. 2010;48:714–715.
168. Collamati A, Martone AM, Poscia A, et al: Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. Aging Clin Exp Res. 2016;28:25–35.
169. Stolzmann KL, Gagnon DR, Brown R, Tun CG, Garshick E. Risk factors for chest illness in chronic spinal cord injury: a prospective study. Am J Phys Med Rehabil. 2010;89:576–583.
170. Spungen AM, Grimm DR, Lesser M, et al: Self-reported prevalence of pulmonary symptoms in subjects with spinal cord injury. Spinal Cord 1997;35:652–657.
171. Gidding SS, Allen NB. Cholesterol and Atherosclerotic Cardiovascular Disease: A Lifelong Problem. J Am Heart Assoc. 2019;8:e012924.
172. von Eckardstein A, Nordestgaard BG, Remaley AT, Catapano AL. High-density lipoprotein revisited: biological functions and clinical relevance. Eur Heart J. 2023;44:1394–1407.
173. La Fountaine MF, Cirnigliaro CM, Kirshblum SC, McKenna C, Bauman WA. Effect of functional sympathetic nervous system impairment of the liver and abdominal visceral adipose tissue on circulating triglyceride-rich lipoproteins. PLoS One. 2017;12:e0173934.
174. O'Meara NM, Devery RA, Owens D, Collins PB, Johnson AH, Tomkin GH. Alterations in cellular cholesterol metabolism following administration of 6-hydroxydopamine to rabbits. Br J Pharmacol. 1992;105:495–499.
175. Mongraw-Chaffin M, Bertoni AG, Golden SH, et al. Association of Low Fasting Glucose and HbA1c with Cardiovascular Disease and Mortality: The MESA Study. J Endocr Soc. 2019;3:892–901.
176. Duckworth WC, Solomon SS, Jallepalli P, Heckemeyer C, Finnern J, Powers A. Glucose intolerance due to insulin resistance in patients with spinal cord injuries. Diabetes. 1980;29:906–910.

177. Bauman WA, Spungen AM. Disorders of carbohydrate and lipid metabolism in veterans with paraplegia or quadriplegia: a model of premature aging. Metabolism. 1994;43:749–756.
178. Stillman MD, Williams S. Guideline for the identification and management of cardiometabolic risk after spinal cord injury: a case of unsubstantiated recommendations. Spinal Cord Ser Cases. 2019;5:97.
179. Nash MS, Groah SL, Gater DR Jr, et al. Identification and Management of Cardiometabolic Risk after Spinal Cord Injury: Clinical Practice Guideline for Health Care Providers. Top Spinal Cord Inj Rehabil. 2018;24:379–423.
180. Després JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk [published correction appears in Arterioscler Thromb Vasc Biol. 2008;28:e151]. Arterioscler Thromb Vasc Biol. 2008;28:1039–1049.
181. Mohebali D, Kaplan D, Carlisle M, Supiano MA, Rondina MT. Alterations in platelet function during aging: clinical correlations with thromboinflammatory disease in older adults. J Am Geriatr Soc. 2014;62:529–535.
182. Popa C, Popa F, Grigorean VT, et al. Vascular dysfunctions following spinal cord injury. J Med Life. 2010;3:275–285.
183. Draghici AE, Taylor JA. Baroreflex autonomic control in human spinal cord injury: Physiology, measurement, and potential alterations. Auton Neurosci. 2018;209:37–42.
184. Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. Sleep Med Rev. 2012;16:47–66.
185. Boudreau P, Yeh WH, Dumont GA, Boivin DB. Circadian variation of heart rate variability across sleep stages. Sleep. 2013;36:1919–1928.
186. Redon J, Lurbe E. Nocturnal blood pressure versus nondipping pattern: what do they mean? Hypertension. 2008;51:41–42.
187. Fritze F, Groß S, Ittermann T, et al. Carotid Lumen Diameter Is Associated With All-Cause Mortality in the General Population. J Am Heart Assoc. 2020;9:e015630.
188. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. Atherosclerosis. 2012;220:128–133.
189. Vik LC, Lannem AM, Rak BM, Stensrud T. Health status of regularly physically active persons with spinal cord injury. Spinal Cord Ser Cases. 2017;3:17099.
190. Hart N, Cramer D, Ward SP, et al. Effect of pattern and severity of respiratory muscle weakness on carbon monoxide gas transfer and lung volumes. Eur Respir J. 2002;20:996–1002.
191. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–968.
192. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53:1801914.

193. Houghton CM, Woodcock AA, Singh D. A comparison of lung function methods for assessing dose-response effects of salbutamol. Br J Clin Pharmacol. 2004;58:134–141.
194. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging. 2006;1:253–260.
195. Savic G, Charlifue S. Aging with Spinal Cord Injury. In: Chhabra HS, editor. ISCoS Textbook on comprehensive management of spinal cord injuries. Haryana, India: Lippincott Williams & Wilkins; 2015. p. 907–917.
196. Srikumar V, Singh U. Respiratory Complications. In: Chhabra HS, editor. ISCoS Textbook on comprehensive management of spinal cord injuries. Haryana, India: Lippincott Williams & Wilkins; 2015. p. 776–782.
197. Gorgey AS, Ennasr AN, Farkas GJ, Gater DR Jr. Anthropometric Prediction of Visceral Adiposity in Persons With Spinal Cord Injury. Top Spinal Cord Inj Rehabil. 2021;27:23–35.
198. Spinal Cord, Guide to Authors [Accessed 2023 October 6]. https://www.nature.com/documents/sc-gta.pdf
199. Jörgensen S. Older Adults With Long-Term Spinal Cord Injury [Doctoral dissertation]. Lund, Sweden, Lund University, Faculty of Medicine, 2017.
200. Satchidanand N, Gunukula SK, Lam WY, et al. Attitudes of healthcare students and professionals toward patients with physical disability: a systematic review. Am J Phys Med Rehabil. 2012;91:533–545.
201. BaumanWA, Raza M, Spungen AM, et al: Cardiac stress testing with thallium-201 imaging reveals silent ischemia in individuals with paraplegia. Arch Phys Med Rehabil. 1994;75:946–950.
202. Arbab-Zadeh A, Fuster V. From Detecting the Vulnerable Plaque to Managing the Vulnerable Patient: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;74:1582–1593.
203. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. Eur J Prev Cardiol. 2017;24:1555–1566.
204. Liu Y, Luo X, Jia H, Yu B. The Effect of Blood Pressure Variability on Coronary Atherosclerosis Plaques. Front Cardiovasc Med. 2022;9:803810.
205. Phillips CL, McEwen BJ, Morel-Kopp MC, et al. Effects of continuous positive airway pressure on coagulability in obstructive sleep apnoea: a randomised, placebo-controlled crossover study. Thorax. 2012;67:639–644.
206. Wyndaele JJ, Kovindha A, Madersbacker H, et al: Neurologic urinary incontinence. Neurourol Urodyn. 2010;29:159–164.
207. Martin Ginis KA, van der Scheer JW, Latimer-Cheung AE, et al. Evidence-based scientific exercise guidelines for adults with spinal cord injury: an update and a new guideline [published correction appears in Spinal Cord. 2018 Oct 4;:]. Spinal Cord. 2018;56:308–321.

208. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. Front Cardiovasc Med. 2018;5:135.
209. Stillman MD, Aston CE, Rabadi MH. Mortality benefit of statin use in traumatic spinal cord injury: a retrospective analysis. Spinal Cord. 2016;54:298–302.
210. Almeida SO, Budoff M. Effect of statins on atherosclerotic plaque. Trends Cardiovasc Med. 2019;29:451–455.
211. Rothwell PM, Howard SC, Dolan E, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol. 2010;9:469–480.
212. Benditt JO. Respiratory Care of Patients With Neuromuscular Disease. Respir Care. 2019;64:679–688.
213. Bonander C, Nilsson A, Björk J, et al. The value of combining individual and small area sociodemographic data for assessing and handling selective participation in cohort studies: Evidence from the Swedish CardioPulmonary bioImage Study. PLoS One. 2022;17:e0265088.
214. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.

Appendix

Questions used to collect data in this thesis are presented:

Study-specific questionnaire

Vilket är ditt nuvarande civiltillstånd? (Endast ett alternativ ska väljas)

- Ogift och ensamboende
- Gift, registrerat partnerskap eller sammanboende
- Skild eller separerad
- Änka/änkling

Vilken är den högsta utbildning du avslutat? Välj det som du tycker stämmer bäst på dig. Ange ett svarsalternativ.

- Ej avslutat grundskola eller annan obligatorisk grundläggande utbildning
- Grundskola, folkskola eller motsvarande (högst 9 år)
- Läroverk, gymnasium, folkhögskola, yrkesutbildning eller motsvarande
- Examen från universitet eller högskola

Vilken är din nuvarande sysselsättning? Du kan ange flera alternativ

- Yrkesarbetar _____% av heltid
- Tjänstledig eller föräldraledig
- Studerar, praktiserar
- Arbetsmarknadsåtgärd
- Arbetslös
- Ålderspensionär
- Avtalspensionär

- Förtidspensionerad, sjukpensionär
- Långtidssjukskriven (mer än 3 månader)
- Övrigt – icke förvärvsarbetande

Tobaksvanor

Röker du? (Endast ett alternativ kan väljas)

- Nej, har aldrig rökt
- Ja, röker regelbundet
- Ja, röker ibland
- Nej, slutade röka år _____

Om du rökt/röker, hur gammal var du när du började röka regelbundet?

År _____

Under de år som du har rökt, hur många cigaretter har du i genomsnitt rökt per dag?

_____antal

Under de år som du har rökt, hur många cigarrer eller cigarrcigaretter har du i genomsnitt rökt per dag?

_____antal

Under de år som du har rökt, hur många gram piptobak har du i genomsnitt rökt per dag?

_____gram

Om du har varit rökare men slutat, svara på följande frågor

Hur många cigaretter rökte du vanligen per dag?

_____antal

Hur många cigarrer eller cigarrcigaretter rökte du vanligen per dag?

_____antal

Hur många gram piptobak rökte du vanligen per dag?

_____gram

Hälso- och sjukdomshistoria

Vilka av dessa sjukdomar har en läkare diagnosticerat på dig alternativt har du blivit kirurgiskt behandlad för? (flera alternativ kan väljas)

- o Hjärtinfarkt/propp i hjärtat
- o Kärlkramp/angina pectoris
- o Förmaksflimmer
- o Hjärtsvikt
- o Klaff-fel på hjärtat
- o By-pass operation eller ballongvidgning av hjärtats kranskärl
- o Åtgärd av förträngningar i pulsåderkärl, t.ex. ben eller halskärl
- o Åtgärd av vidgning av stora kroppspulsådern (aorta)
- o Stroke/slaganfall/hjärninfarkt/propp i hjärnan/hjärnblödning
- o Högt blodtryck
- o Höga blodfetter/kolesterol
- o Diabetes/sockersjuka
- o Kroniskt obstruktiv lungsjukdom (KOL), kronisk bronkit eller emfysem
- o Astma
- o Annan lungsjukdom (annat än astma, kroniskt obstruktiv lungsjukdom (KOL), kronisk bronkit eller emfysem
- o Tuberkulos
- o Sömnapné
- o Glutenintolerans/celiaki
- o Morbus Crohn eller ulcerös kolit
- o Reumatisk sjukdom t.ex. reumatoid artrit/Bechterews sjukdom/Psoriasisartrit/SLE/Sjögrens syndrom

- Cancer
- Inga av ovanstående sjukdomar

Luftvägar

Brukar du hosta även när du inte samtidigt är förkyld?

- Ja
- Nej

Hostar du de flesta dagar under minst tre månader varje år?

- Ja
- Nej

I hur många år har du haft denna hosta?

- Mindre än 2 år
- 2-5 år
- Mer än 5 år

Brukar du hosta upp slem eller har du slem i bröstet som du har svårt att få upp när du inte samtidigt är förkyld?

- Ja
- Nej

Får du upp slem eller har du problem med slem i bröstet på det viset de flesta dagar under minst tre månader varje år?

- Ja
- Nej

I hur många år har du haft dessa slemproblem?

- Mindre än 2 år
- 2-5 år

- Mer än 5 år

Använder du hostmaskin?

- Ja, dagligen
- Ja, flera gånger per vecka
- Ja, men endast ”vid behov”
- Nej

Brukar du ha pip eller väsningar i bröstet när du andas?

- Ja
- Nej

Om du svarade ”ja”:

Har du haft pip eller har det väst i bröstet vid något tillfälle under de senaste 12 månaderna?

- Ja
- Nej

Under de senaste 12 månaderna, har du haft detta pip eller väsning i bröstet bara när du samtidigt varit förkyld?

- Ja
- Nej

Under de senaste 12 månaderna, har du haft någon attack av väsningar eller pipande samtidigt som du känt andnöd?

- Ja
- Nej

Besväras du av andnöd när du har bråttom och kör rullstol på plan mark eller för en mindre sluttning?

- Ja
- Nej

Om du svarade ”ja”:

Måste du stanna för att andas när du kör rullstol på plan mark i din egen takt?

- Ja
- Nej

Måste du stanna för att andas när du kör rullstol efter några minuter på plan mark?

- Ja
- Nej

Är du alltför andfådd för att kunna lämna hemmet, eller blir du andfådd av att klä av eller på dig?

- Ja
- Nej

Hjärt- och kärlsjukdom

Får du smärtor, stickningar eller ont i bröstet när du kör rullstol i mindre sluttningar, eller fort på plan mark?

- Ja
- Nej

Får du smärtor, stickningar eller ont i bröstet när du kör rullstol i vanlig takt på plan mark?

- Ja
- Nej

Om du svarade ”ja” på någon av frågorna 40 och 41 fyll i följdfrågor 42-44

Om du får smärtor eller obehag i bröstet i samband med att du rör på dig, brukar du då:

- Stanna
- Sakta ner farten
- Fortsätta i samma takt?

Om du stannar eller saktar ner, hur lång tid tar det innan smärtan försvinner?

- Omedelbart
- Efter mindre än 10 minuter
- Efter mer än 10 minuter
- Smärtan finns kvar under lång tid

Har du någon gång haft svår smärta i bröstet som varat i en halvtimme eller mer?

- Ja
- Nej

Mediciner

Har du tagit någon av följande mediciner de senaste 2 veckorna?

Alvedon, Panodil, Reliv (paracetamol)

- Ungefär en gång i veckan
- Flera gånger i veckan
- Ungefär en gång om dagen
- Flera gånger om dagen

Ipren, Ibumetin (ibuprofen)

- Ungefär en gång i veckan
- Flera gånger i veckan
- Ungefär en gång om dagen
- Flera gånger om dagen

Voltaren, Diklofenak (diklofenak)

- Ungefär en gång i veckan
- Flera gånger i veckan
- Ungefär en gång om dagen
- Flera gånger om dagen

Treo, Magnecyl, Albyl minor (acetylsalicylsyra)

- Ungefär en gång i veckan
- Flera gånger i veckan
- Ungefär en gång om dagen
- Flera gånger om dagen

Tar du regelbundet receptbelagda läkemedel för någon sjukdom?

- Ja
- Nej

Vilka läkemedel?

_____

_____

_____

Fysisk aktivitet

Hur mycket rör du dig och anstränger dig kroppsligt på fritiden under de senaste 12 månaderna?

- Stillasittande fritid Du ägnar dig mest åt läsning, TV, datorer eller annan stillasittande sysselsättning på fritiden. Du gör hushållsarbete, kör manuell- eller el-rullstol utanför hemmet mindre än 2 timmar i veckan.
- Måttlig motion på fritiden Du kör manuell- eller el-rullstol utanför hemmet, tyngre hushållsarbete, ordinärt trädgårdsarbete minst 4 timmar i veckan.
- Måttlig men regelbunden motion på fritiden Du ägnar dig åt t.ex. rullstolskörning, gymträning, motionsgymnastik eller tyngre trädgårdsarbete minst 1-2 tillfällen per vecka minst 30 minuter per gång totalt 2-3 timmar i veckan. Varje tillfälle varar minst 30 minuter per gång.
- Regelbunden motion och träning Du ägnar dig åt t.ex. hård träning eller tävling i parasport, rullstolskörning, gymträning, motionsgymnastik regelbundet och flera gånger i veckan. Minst 3 tillfällen per vecka. Varje tillfälle varar minst 30 minuter per gång.

ADFSCI

1 Har du tillfällen med autonom dysreflexi (AD) (ett tillstånd då blodtrycket stiger väldigt snabbt, ofta p.g.a. ett smärtsamt stimuli nedanför din skadenivå, resulterande i symtom såsom huvudvärk, svettningar, gåshud)?

- o Ja
- o Nej
- o Vet ej

För fråga 11-15, vänligen använd skalan nedan för att skatta ***hur ofta du får symtom****:*

0: aldrig 1: sällan 2: ibland 3: ofta 4: väldigt ofta

11 Hur ofta upplever du dessa symtom under dagen?

0	1	2	3	4	
					Svindel
					Yrsel
					Dimsyn
					Illamående
					Svaghet
					Förvirring
					Utmattning
					Svimning

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Spinal cord injury is a rare and multifaceted condition with great improvement in longevity during the 20th century. In recent decades this improvement has abated due to cardiovascular and respiratory diseases occurring prematurely. People with cervical and upper thoracic spinal cord injuries have the lowest life expectancy. An increased knowledge of cardiopulmonary health in long-term spinal cord injury is paramount for further improvement in longevity.

This thesis aim was to comprehensively describe the function and structure of the cardiopulmonary systems in middle-aged people with cervical and upper thoracic spinal cord injuries, on average three decades after their injury. The findings are compared with matched controls from the general population. The results provide a deeper and broader clinical understanding of cardiopulmonary health in this population, which can be used in the clinical setting, and directions for future research efforts to improve longevity.

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