Respiratory Function after Spinal Cord Injury

changes over time, consequences and effect of training

Karin Postma

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Ademhalingsfunctie na een dwarslaesie
beloop, gevolgen en effect van training

ERASMUS UNIVERSITEIT ROTTERDAM

PROMOTIECOMMISSIE

Promotor: Prof.dr. H.J. Stam

Overige leden: Prof.dr. J. Bakker

Prof.dr. C.M.F. Dirven

Prof.dr. L.H.V. van der Woude

Copromotor: Dr. J.B.J. Bussmann

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Chapter **1**

General introduction

SPINAL CORD INJURY

A spinal cord injury (SCI) is defined as a disruption of the spinal cord resulting in loss of motor, sensory and autonomic function below the level of lesion. The neurological level and completeness of the injury determine the degree of impairment.[1] Lesion level is roughly divided into tetraplegia (or quadriplegia) and paraplegia (Figure 1). With tetraplegia the arms, trunk, legs and pelvic organs are involved. With paraplegia the arms are spared, but depending on the level of injury, the trunk, legs, and pelvic organs may be involved. Completeness of lesion is described by the American Spinal Injury Association (ASIA) Impairment scale (AIS), and ranges from A to E (Table 1).[1]
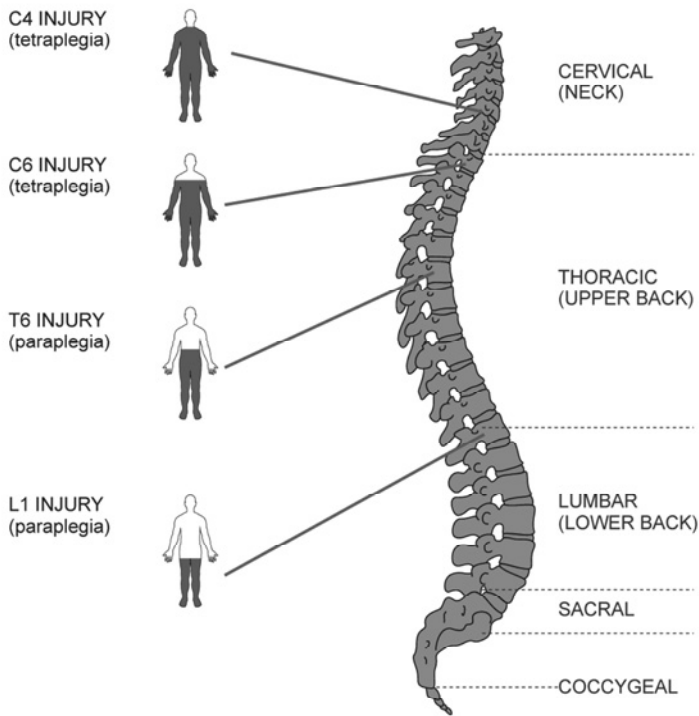
Figure 1. Levels of injury (from Southern Spinal Injuries Trust, http://www.sitt.org.uk with permission; re-use is not permitted).

The cause of injury can be traumatic (e.g. due to traffic, falls, sports or leisure activities) or non-traumatic (e.g. due to vascular diseases, spinal degeneration, inflammation, or tumors). The worldwide incidence of traumatic SCI was recently estimated at 23 cases per million persons.[2] Estimates for non-traumatic SCI vary between 6 (Western Europe) and 76 (North America) per million per year per region.[3] In the Netherlands the incidence of SCI is at the low range of worldwide incidence rates: 14 per million per

year for traumatic SCI[4] and 8 per million for non-traumatic SCI.[5] Survival after SCI has improved in the last decades, but mortality is still up to three times higher than in the general population, mainly due to medical complications.[6]

Table 1. The American Spinal Injury Association Impairment scale (AIS)

A = Complete	No sensory or motor function is preserved in the sacral segments S4-S5.
B = Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5, AND no motor function is preserved more than three levels below the motor level on either side of the body.
C = Motor incomplete	Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a grade less than 3.
D = Motor incomplete	Motor function is preserved below the neurological level, and at least half of key muscle functions below the single neurological level of injury have a muscle grade > 3.
E = Normal	Sensation and motor function are graded as normal in all segments.

The majority of persons with newly acquired SCI in the Netherlands are, after several days to several weeks, transferred from the hospital to one of the eight rehabilitation centers specialized in SCI rehabilitation for further treatment.[4] Others are transferred to a rehabilitation center not specialized in SCI, a nursing home, or to their own home. Between 2002 and 2007, most persons admitted to one of the SCI-specialized rehabilitation centers in the Netherlands or Flanders (Belgium) were male (63%), had a non-traumatic injury (55%), paraplegia (64%), and a motor incomplete lesion (62%). The median (interquartile range) length of stay at the inpatient rehabilitation setting was 156 days (77-256).[7]

RESPIRATORY FUNCTION

The function of the respiratory system is to provide for the exchange of oxygen and carbon dioxide between the human body and the environment. The act of breathing causes air to go in and out of the lungs where gas exchange, to and from the blood takes place. Normal breathing at rest is accomplished almost entirely by contraction and relaxation of the diaphragm.[8] During inspiration, contraction of the diaphragm pulls the lower surfaces of the lungs downward. Then, during expiration, the diaphragm relaxes and the elastic recoil of the lungs, chest wall, and abdominal structures compresses the lungs. During deep inspiration the lungs are expanded further by raising the ribcage by contraction of the external intercostal muscles, the sternocleidomastoid muscles, the scalenes and, if necessary, the upper trapezius muscle. In addition, increased intra-abdominal pressure pushes the lower part of the ribcage up and out. During heavy breathing (as in exercise) and coughing, expiration becomes active by contraction of the abdominal muscles, internal intercostal muscles, pectorals, and the latissimus dorsi.[8]

Effect of spinal cord injury on respiratory function

Injury of the spinal cord at or above the thoracic 12 segment causes (partial) paralysis of respiratory muscles, which in turn causes impaired respiratory function. The higher and more complete the lesion, the more respiratory muscles are impaired. Figure 2 shows the muscles involved in breathing and their level of innervation. Persons with low paraplegia have weakness of the abdominal muscles. In high paraplegia the intercostal muscles are also affected. In persons with low tetraplegia almost all expiratory muscles and some of the accessory inspiratory muscles are involved. In persons with lesions above the level of the phrenic nerve, which arises from the segments C3 to C5, the diaphragm is (partially) paralyzed.

In persons who survive the acute phase after SCI, respiratory muscle strength and pulmonary function recovers to some extent in the months thereafter.[9, 10] Recovery can continue up to a year after rehabilitation, but at some point after onset, the initial improvement seems to turn into a decline that surpasses the normal age-related decline.[11, 12] So far it is unclear when, and in which persons, the initial improvement turns into a decline that surpasses the normal age-related decline.
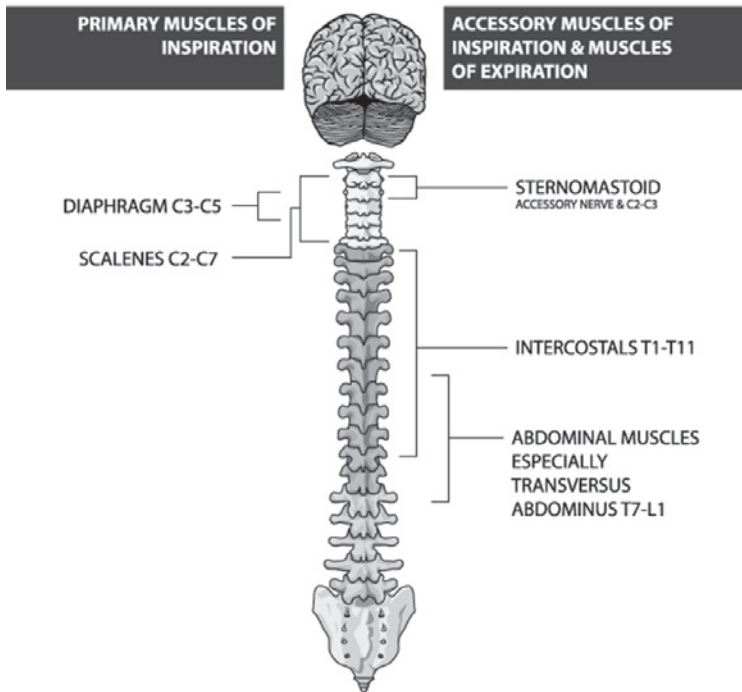

Figure 2. Muscles of breathing and their innervation (from http://www.eprimarycare.onf.org with permission).

Consequences of impaired respiratory function

Figure 3 shows a schematic representation of the consequences of impaired respiratory function. This scheme also represents the theoretical background of this thesis. Loss of function of the inspiratory and expiratory muscles may affect breathing, cough capacity, exercise capacity, pulmonary function, and perceived respiratory function. Impaired breathing may alter the breathing pattern, causing shallow breathing (or hypoventilation), increased work of breathing, sensation of breathlessness, lower exercise capacity, or even the inability to breathe without support. [13, 14, 15] In addition, speech may be affected as noticed by breathlessness while talking, a weak voice, the inability to raise one's voice, and interruption of speech for inspiration.[16] Furthermore, the lack of regular deep inspiration may lead to increased stiffness of lung tissue and chest wall.[17] Impaired cough may lead to the inability to clean the lungs and airways from foreign material (during aspiration) and secretions (during infection).[18] Impaired ability to breathe deeply and expire forcefully results in impaired pulmonary function, as measured by pulmonary function tests (lung volumes and flows).

Hypoventilation and impaired cough contribute to the development of respiratory complications such as sputum retention, atelectasis, pneumonia, and respiratory failure. These complications can easily become serious, lead to hospitalization and may even become life-threatening.[19, 20] Despite improved medical management over the last decades, respiratory complications are still a common cause of mortality in persons with SCI.[21-25] Therefore, minimizing the risk of respiratory complications is an important goal in SCI care.
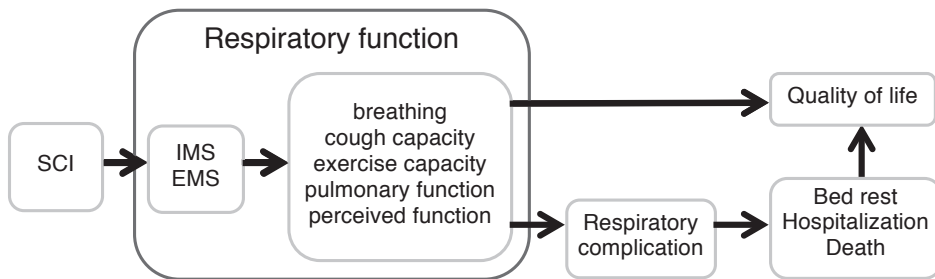
Figure 3. Schematic representation of the relationships hypothesized in this thesis. Abbreviations: SCI=spinal cord injury, IMS=inspiratory muscle strength, EMS=expiratory muscle strength.

Finally, impaired respiratory function may have direct or indirect consequences on someone's life in general. For example, difficulty with talking may place a person in social isolation or affect him or her professionally, increased effort of breathing or dyspnea may affect a person in his or her activities or cause emotional stress, and a decreased ability to cough can make a person insecure. Signs of impaired respiratory function or consequences of respiratory complications (bed rest, hospitalization) may affect someone's feeling of wellbeing. In addition, there may be a direct relationships between low pulmonary

function and lower quality of life.[26-28] Altogether, research in this field is scarce, and little is known about the extent and the direction of relationships between respiratory function, respiratory complications, and quality of life.

Respiratory management

Current practice of respiratory care in persons with SCI is mainly based on clinical experience and expert opinion.[29, 30] The main goal of respiratory management during (sub)acute care is to achieve independent breathing and prevent respiratory complications such as secretion retention, atelectasis, and lower tract respiratory infection. In a later phase, when persons breathe independently and respiratory function appears to be stable, respiratory care tends to move to the background and mainly consists of responding to emergent respiratory complications such as infections. This strategy may not be optimal. After all, as described above, respiratory complications such as respiratory infections continue to be an important cause of hospitalization and early death in persons with chronic SCI. Undetected excessive decline of pulmonary function in chronic SCI may be one of the reasons that mortality rates remain high despite improved critical care.[22, 31] Adding specific training to improve respiratory function during inpatient rehabilitation, and structuring follow-up care to monitor changes and apply adequate preventive care after rehabilitation, may lower the risk of respiratory complications.

THE UMBRELLA AND SPIQUE PROJECT

Part of this thesis is based on data from a Dutch multicenter prospective cohort study, the Umbrella project and an extra follow-up measurement, the SPIQUE project. Both projects are part of the Dutch research program "Physical strain, work capacity and mechanisms of restoration of mobility in the rehabilitation of individuals with SCI", funded by ZON-Rehabilitation program (http://www.scionn.nl). In the Umbrella project, 225 persons were included between August 2000 and July 2003.[32] Persons were eligible for inclusion if they were admitted for initial inpatient rehabilitation to one of the 8 participating rehabilitation centers with specialized SCI units in the Netherlands, classified as grade A, B, C, or D on the American Spinal Injury Association Impairment Scale (AIS), between 18 and 65 years of age, and expected to remain (at least in part) wheelchair dependent. Persons with a progressive disease (such as a malignant tumor) or a psychiatric problem, and those who did not sufficiently comprehend the Dutch language were excluded. An extensive measurement protocol was administered to determine lesion characteristics, co-morbidity, physical capacity, basic skills, daily functioning, quality of life, demographics and psychosocial factors. Persons were tested at several occasions during and after inpatient rehabilitation. For this thesis we used data of 4 test occasions: the start of active rehabilitation, at discharge from the inpatient setting, and 1 and 5 years after discharge.

AIMS AND OUTLINE OF THE PRESENT THESIS

The general aim of this thesis was to gain insight into respiratory function in the first years after SCI. We studied respiratory function, changes over time, consequences of impaired respiratory function and the effects of an added respiratory training program.

In **Chapter 2** we studied whether pulmonary function at discharge from inpatient rehabilitation can predict respiratory infection in SCI in the first year after discharge. In addition, we studied which pulmonary function parameter is most predictive. **Chapter 3** describes changes in pulmonary function during inpatient rehabilitation and the first 5 years thereafter. In addition, we studied whether modifiable factors such as smoking, inspiratory muscle strength, body mass index, physical fitness, and activity level were associated with change of pulmonary function after inpatient rehabilitation. **Chapter 4** focuses on the prevalence of impaired respiratory function, incidence of respiratory infections and associations among these parameters in persons with SCI 5 years after initial inpatient rehabilitation. In addition, associations between impaired respiratory function and health-related quality of life were assessed. In **Chapter 5** the results of a randomized controlled trial we conducted are described. In this trial the immediate and long-term effects of resistive inspiratory muscle training on respiratory function, respiratory complications, and HRQOL in persons with SCI were studied. In addition, data of this trial is used to study longitudinal relationships between respiratory muscle strength and cough capacity in **Chapter 6.** Finally, in **Chapter 7** the main findings are summarized and discussed.

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Chapter 2

Predicting respiratory infection one year after inpatient rehabilitation with pulmonary function measured at discharge in persons with spinal cord injury

Karin Postma
Johannes B.J. Bussmann
Janneke A. Haisma
Lucas H.V. van der Woude
Michael P. Bergen
Henk J. Stam

ABSTRACT

Objective: To determine whether pulmonary function at discharge from inpatient rehabilitation can predict respiratory infection in spinal cord injury in the first year after discharge, and to determine which pulmonary function parameter predicts best.

Design: Multicenter prospective cohort study.

Subjects: A total of 140 persons with spinal cord injury.

Methods: Pulmonary function was tested at discharge from inpatient rehabilitation. Pulmonary function parameters (expressed in absolute and percentage predicted values) were: forced vital capacity, forced expiratory volume in 1 sec, and peak expiratory flow. Respiratory infection was determined one year after discharge by a physician. Differences between the respiratory infection and non-respiratory infection groups were tested; and receiver operating characteristic curves were used to determine how accurately pulmonary function parameters could predict respiratory infection.

Results: Of the 140 participants, 14 (10%) experienced respiratory infection in the first year after discharge. All pulmonary function parameters were significantly lower in persons who experienced respiratory infection than in those who did not. All pulmonary function parameters were almost equally accurate in predicting respiratory infection; only percentage predicted forced vital capacity was less accurate.

Conclusion: Pulmonary function at discharge from inpatient rehabilitation can be used as a predictor of respiratory infection in the first year after discharge in spinal cord injury. No single pulmonary function parameter was a clearly superior predictor of respiratory infection.

INTRODUCTION

Although the life expectancy of persons with spinal cord injury (SCI) has improved in recent decades, this group is still prone to long-term secondary medical complications.[1-4] Respiratory complications, such as respiratory infection (RI) and atelectasis, are some of the more serious long-term secondary medical complications in persons with SCI.[2, 5] Long-term respiratory complications are a common cause of hospitalization[6] and a major cause of mortality.[3, 4] Therefore, minimizing the risk of long-term respiratory complications should be an important goal of primary SCI rehabilitation and aftercare.[7]

To minimize the risk of long-term respiratory complications it is important to identify persons at risk during primary rehabilitation. Persons with SCI who are neurologically the most impaired (i.e. those with complete high tetraplegia) are at greatest risk of respiratory complications.[2] A logical explanation for this finding is that this latter group is also the most restricted in pulmonary function (vital capacity, cough, and respiratory muscle strength).[8-11] However, the relationship between lesion characteristics and pulmonary function is not straight forward: respiratory complications are not only restricted to complete tetraplegia, and pulmonary function varies strongly within different lesion groups. For example, Linn et al[9] suggested that, within any given level of injury, it is likely that smaller vital capacity means a greater risk of respiratory complications and early death. From this point of view, pulmonary function has the potential to be a better predictor than lesion characteristics. Compared with lesion characteristics, another advantage of pulmonary function is that it is a modifiable factor that, clinically, can make it a more useful predictor. If pulmonary function is predictive of respiratory complications, it can be used not only to identify persons at risk in an early stage and as an alarm for preventive strategies, but also as the central topic in a specific training program focusing on decreasing the risk of long-term respiratory complications.

The aim of the present study was to determine whether pulmonary function at discharge from inpatient rehabilitation can predict RI in SCI within the first year after discharge. Additionally, to determine which pulmonary function parameter can best predict RI.

MATERIALS AND METHODS

For this study, data of a Dutch multicenter prospective cohort study on the restoration of mobility during SCI rehabilitation were used.[12, 13]

Subjects

In the Dutch multicenter study, persons with SCI admitted for primary rehabilitation to one of the 8 participating rehabilitation centers from August 2000 to July 2003 were included if they were between 18 and 65 years of age and were expected to remain (at least in part) wheelchair-dependent. Subjects were excluded if they had a progressive disease, a psychiatric condition interfering with constructive participation, or if they did not sufficiently comprehend the Dutch language. The study was approved

by the medical ethics committee, and prior to participation all subjects gave their written informed consent. For the present study we included persons who were still enrolled in the Dutch multicenter study at discharge from inpatient rehabilitation.

Pulmonary function

Pulmonary function (PF) was determined at discharge from inpatient rehabilitation by forced spirometry measurements with the Oxycon Delta® (Jaeger, Hoechberg, Germany). Persons were tested seated in a wheelchair and wearing a nose clip. Three repeated flow volume curves were made; in case of a non-characteristic curve, an extra measurement was performed.[14] The best trial, determined as the trial with the highest sum of forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1), was used in further analysis. The FVC, FEV_1 and peak expiratory flow (PEF) were expressed in absolute values and percentage of the predicted values (based on able-bodied persons of the same age, gender, and height).

Respiratory infection

A physician determined one year after discharge from inpatient rehabilitation, whether the subject had had RI since discharge and how many days they stayed in bed due to RI. This was done by means of a custom-made questionnaire on secondary complications. Physicians were instructed that only clinically important infections, not a simple nose or head cold, were to be counted as RI.

Personal and lesion characteristics

Age, gender, body weight, body mass index (BMI) (i.e. body weight (kg)/height (m^2)), smoking status, level and completeness of lesion were established at discharge from inpatient rehabilitation. A person was defined as a smoker when he or she smoked prior to the onset of SCI. Level and completeness of lesion were determined according to the International Standards for Neurological and Functional Classification of Spinal Cord Injury.[15] Persons were diagnosed with tetraplegia in case of impairment or loss of function at the cervical segments of the spinal cord, and with paraplegia in case of impairment or loss of function at the thoracic, lumbar or sacral segments. The lesion was defined as complete when motor function was absent (American Spinal Injury Association (ASIA) category A or B), and incomplete when motor function was preserved in the lowest sacral segment (ASIA category C or D).

Statistical analyses

Analysis was performed with SPSS 12.0. Data are presented as mean and standard deviation. Data on the incidence of RI were analyzed in a descriptive way. Based on the occurrence of RI (yes/no), 2 sub-groups were created. These subgroups were tested on differences in person-related and lesion-related characteristics (Phi-Cramers'V for nominal and Mann-Whitney U test for continuous values). Differences in PF between the group with and without RI were tested with the Mann-Whitney U test. $P<.05$ was considered significant.

Receiver operating characteristic (ROC) curves were constructed for all PF parameters, considering the occurrence of RI as the dependent parameter.[16, 17] The accompanying area under the curve (AUC) was calculated to determine how accurately the different PF parameters could predict the occurrence of RI one year after rehabilitation discharge. A parameter with AUC=100% was considered a perfect predictor, 90%<AUC≤100% highly accurate, 70%<AUC≤90% moderately accurate, 50%<AUC≤70% less accurate, and AUC=50% a non-informative predictor.[18] Subsequently, for each parameter a cut-off value was determined (based on the highest sum of sensitivity and specificity), and the corresponding sensitivity, specificity and positive predictive value (PPV) and negative predictive value (NPV) were calculated.

RESULTS

At discharge from inpatient rehabilitation, 199 persons were still enrolled in the Dutch multicenter study. Pulmonary function at discharge was missing in 20 persons and 39 persons did not participate in the measurements one year after discharge. As a result, in 140 persons PF at discharge and RI one year after discharge from inpatient rehabilitation was known and used for analyses in the present study. Analysis showed no significant differences in person-related and lesion-related characteristics, between persons who were tested at discharge for PF and persons who were not. Also, there were no significant differences found in PF, person-related and lesion-related characteristics, between persons who were used for the final analyses of this study and persons who dropped out because they did not participate in the measurements one year after discharge. Table 1 shows the patient characteristics; none of these persons were ventilator dependent.

Table 1. Population characteristics and comparison of age, body weight, body mass index (BMI), gender, smoking status, level and completeness of lesion (all measured at discharge) in persons with and without respiratory infection (RI) in the first year after discharge from inpatient rehabilitation

	Total population (n=140)	Persons with RI (n=14)	Persons without RI (n=126)	P*
Age, years, mean (SD)	39.9 (13.8)	44.3 (14.1)	39.4 (13.7)	.224
Body weight, kg, mean (SD)	74.7 (14.8)	76.4 (14.2)	74.6 (14.9)	.677
BMI, kg/m^2, mean (SD)	23.6 (4.1)	25.2 (4.6)	23.4 (4.0)	.130
Gender, male, %	72.1	50.0	74.6	.051
Smokers, %	45.3	42.9	45.5	.849
Level of lesion, tetraplegia, %	36.7	57.1	34.4	.094
Completeness of lesion, complete, %	67.2	76.9	66.2	.430

*Differences between subgroups were tested with Phi-Cramers' V (nominal values) and the Mann-Whitney U test (continuous values). SD=standard deviation.

Fourteen of the 140 persons (10%) experienced RI in the first year after discharge from inpatient reha-bilitation; 9 persons stayed in bed for at least one day (1, 2, 3, 5, 10, 10, 14, 18 and 40 days) because of

RI. Of these, 2 were hospitalized. Gender and level of lesion tended to be different between the groups (relatively more females and more tetraplegia in the RI group). The RI group did not differ from the non-RI group with respect to age, weight, BMI, smoking, or completeness of lesion (Table 1).

All PF parameters were significantly (P<.05) lower in persons who experienced RI in the first year after discharge from inpatient rehabilitation than in those who did not (Table 2).

Almost all PF parameters had an AUC between 70% and 90% and therefore can be considered moderately accurate predictors; according to our definitions only percentage predicted FVC was a less accurate predictor (Table 3). Figure 1 presents the ROC curve and the AUC of FEV_1.

Table 2. Comparison of pulmonary function at discharge in persons with and without respiratory infection (RI) in the first year after discharge from inpatient rehabilitation

	Total population (n=140)	Persons with RI (n=14)	Persons without RI (n=126)	P*
FVC, l	3.91 (1.28)	3.08 (1.53)	4.00 (1.22)	.003
FVC, % predicted†	84.24 (22.86)	71.04 (23.83)	85.70 (22.36)	.026
FEV1, l	3.17 (1.01)	2.35 (1.00)	3.27 (0.98)	.001
FEV1, % predicted†	82.34 (21.44)	65.29 (17.95)	84.23 (21.01)	.001
PEF, l/sec	5.65 (1.88)	3.96 (1.60)	5.84 (1.82)	.001
PEF, % predicted†	63.92 (19.37)	47.73 (16.93)	65.72 (18.84)	.001

Data are presented as mean (standard deviation). *Differences between subgroups were tested with the Mann-Whitney U test. †Based on able-bodied persons of same age, gender, and height. FVC=forced vital capacity; FEV1=forced expiratory volume in 1 sec; PEF=peak expiratory flow.

DISCUSSION

This study shows that PF at discharge from inpatient rehabilitation can be used to identify persons with SCI at risk of developing RI within the first year after discharge. Persons who developed RI had significantly lower PF than the others, and most PF parameters can be considered moderately accurate predictors of RI.

Our results are in agreement with other studies exploring respiratory complications in patients with neuromuscular disorders other than SCI.[19, 20] Both of these last studies identified inspiratory vital capacity (IVC) as one of the predictors (besides peak cough flow and maximal inspiratory pressure, respectively) of severe chest infection in children with neuromuscular disorders, and sleep-disordered breathing in adults with neuromuscular disorders, respectively. IVC is a measure of vital lung capacity and is comparable to FVC in our study. In the study of Dohna et al[19] and Ragette et al,[20] IVC was a stronger predictor than in our study, probably because persons in their study groups had lower mean PF and a higher incidence of illness.

Table 3. Predictors of respiratory infection in the first year after discharge from inpatient rehabilitation, with area under the curve (AUC) and cut-off point based on highest sum of sensitivity and specificity. Sensitivity (Se), Specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) are presented for the given cut-off points

	AUC (%)	Cut-off point	Se (%)	Sp (%)	PPV (%)	NPV (%)
FVC, l	74	3.2	78.6	73.8	25.0	96.9
FVC, % predicted	68	77	71.4	66.7	19.2	95.5
FEV1, l	78	2.5	78.6	75.4	26.2	96.9
FEV1, % predicted	76	70	71.4	74.6	23.8	95.9
PEF, l/sec	78	4.7	78.6	73.0	24.4	96.8
PEF, % predicted	76	51	64.3	79.4	25.7	95.2

FVC, FEV1 and PEF were measured at discharge and expressed in absolute values and percentage of predicted (% predicted) values based on able-bodied persons of same age, gender, and height. FVC=forced vital capacity; FEV1=forced expiratory volume in 1 sec; PEF=peak expiratory flow.

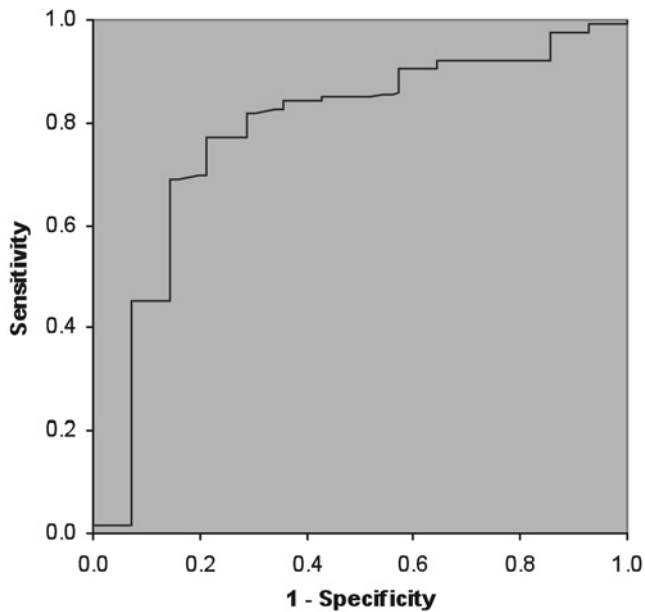**Figure 1.** Receiver operator characteristics (ROC) curve with accompanying area under the curve (AUC) of forced expiratory volume in 1 sec (l).

Respiratory problems and complications are often thought to be a problem for persons with tetraplegia only. Although we found a (non-significant) tendency for more persons with tetraplegia than persons with paraplegia to experience RI, the occurrence of RI was not restricted to tetraplegia. Therefore, the results of our study indicate that PF is a stronger predictor of RI than lesion level, and programs aimed at the prevention and treatment of RI should target not only persons with tetraplegia but also those with paraplegia and low PF.

In the RI group we were surprised to find a tendency for relatively more females than males. Because healthy females have lower PF (absolute values) compared with males,[21] a similar percentile decrease following SCI might cause PF to reach a certain absolute cut-off value and therefore lead to an earlier increased risk of RI in females compared with males. Other possible determinants of RI (e.g. age, body weight, BMI, smoking and completeness of lesion) showed no significant difference between the RI and non-RI group. Other factors that we did not explore (e.g. the level of physical activity) might also have influenced the risk of RI.

In this study we also investigated which PF parameter can best be used to predict RI. However, no single PF parameter appeared to be clearly superior to the other PF parameters in predicting RI. As in previous studies,[22] all PF parameters in the present study were highly correlated with each other; correlation coefficients ranged from 0.48 to 0.92 ($P<.001$). All the PF parameters showed a significant difference between the RI and non-RI group, and the ROC curves were similar. Most of the PF parameters had an AUC between 70% and 90%, which makes them "moderately accurate" predictors.[18] Only percentage predicted FVC appeared to be a weaker predictor, indicated by an AUC below 70%.

To explain the predictive characteristics of the PF parameters, we used FEV_1 (liters) as an example. An FEV_1 with a cut-off point of 2.5 l has a good sensitivity and a good specificity in predicting RI. Also the positive predictive value is high, meaning that just over one-quarter (26.2%) of persons with an FEV_1 below 2.5 l actually experienced RI within one year after discharge. However, 21.4% (1-Se) of persons who experienced RI would have been missed. Since RI is a serious complication, possibly leading to hospitalization or even death, a higher cut-off point can be considered in future treatment protocols.[16] A cut-off point of 2.8 l FEV_1, for example, will lead to higher sensitivity (85.7%) and lower specificity (67.5%). Although, more persons will be falsely identified as being at risk of developing RI, more importantly, fewer at risk will be missed.

A limitation of our study is that the incidence of RI was determined retrospectively by anamnestic information, without precise criteria. RI is a rather wide diagnostic term, which includes upper and lower tract infection. Even though the participating physicians were instructed that only clinically important infections were to be counted as RI, differences in interpretation between physicians may have occurred in the less serious cases. A former study, including only radiographically confirmed pneumonia (infection of lung tissue) and/or atelectasis (airlessness within the lung), showed a lower (3.5 vs 10%) incidence one year after discharge.[2] This supports the idea that, in some cases, less severe infections are also included in our study. To investigate if this could have confounded our results, we also performed analyses in which only persons who stayed in bed at least one day because of infection were defined as having RI. These analyses showed an incidence of 6.4%, which is closer to that reported by McKinley et al.[2] Moreover, the earlier described results became more profound; differences in PF between the RI and non-RI groups were significant and the ROC curves improved, resulting in higher AUCs. Thus, PF at discharge from inpatient rehabilitation might be an even stronger predictor for the more severe RI in SCI after discharge.

A second limitation of the present study is the small number of persons with RI in the study group; this is attributed to the relatively low incidence of this complication, and the short follow-up period. Sub-groups of approximately equal size would have enabled the use of multi-factorial analysis that included several factors at the same time (including PF, lesion characteristics, and perhaps physical activity), which might have resulted in a more accurate prediction model.

Finally, of 199 persons still enrolled in the Dutch multicenter study at discharge from inpatient rehabilitation, we excluded 59 persons because PF was missing or they did not participate in the measurements one year after discharge. Analysis between groups did not show significant differences between persons used for the present study and the persons excluded. A considerable part of the loss to follow-up was due to the small number of persons that participated in the measurements after discharge from the rehabilitation centre.[12] Although the precise reasons for not participating after discharge are unknown, they were widely diverse. Verbal reports ranged from being too busy with work and/or social life to make time for the measurements, to not feeling well enough to travel to the rehabilitation center and perform the tests. Therefore, we have no indication whether the loss to follow-up after discharge led to a specific selection and thereby influenced the results of the study.

In conclusion, PF at discharge from inpatient rehabilitation can be used as a predictor of respiratory infection in the first year after discharge in SCI. FVC (l), FEV_1 (l or % predicted) and PEF (l/sec or % predicted) are moderately accurate predictors. We recommend testing PF during primary rehabilitation, to identify persons at risk of developing RI. Not only persons with tetraplegia, but also persons with paraplegia and low PF (e.g. $FEV_1 < 2.5$ l) should be instructed in preventive strategies and monitored after discharge for changes in pulmonary status. Future studies should focus on decreasing the risk of long-term respiratory complications by improving PF with specific training. At present, a follow-up study of the current cohort is in progress; this study will investigate changes in PF and respiratory complications 5 years after discharge from inpatient rehabilitation.

ACKNOWLEDGEMENT

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Chapter 3

Changes in pulmonary function during the early years after inpatient rehabilitation in persons with spinal cord injury: a prospective cohort study

Karin Postma
Janneke A. Haisma
Sonja de Groot
Maria T.E. Hopman
Michael P. Bergen
Henk J. Stam
Johannes B.J. Bussmann

ABSTRACT

Objective: To describe changes in pulmonary function (PF) during the 5 years after inpatient rehabilitation in persons with spinal cord injury (SCI) and to study potential determinants of change.

Design: Prospective cohort study.

Setting: Eight rehabilitation centers with specialized SCI units.

Participants: Persons with SCI (N=180).

Interventions: Not applicable.

Main Outcome Measures: PF was determined by forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) as a percentage of the predicted value, at the start of rehabilitation, at discharge, and 1 and 5 years after discharge from inpatient rehabilitation. The population was divided into 3 subgroups based on whether their PF declined, stabilized, or improved.

Results: FVC improved on average 5.1% over the whole period between discharge of inpatient rehabilitation and 5 years thereafter, but changes differed largely between persons. FVC declined in 14.9% of the population during the first year after discharge. During this year, body mass index, inspiratory muscle strength, change in peak power output, and change in peak oxygen uptake differed significantly between subgroups. FVC declined in 28.3% of the population during the following 4 years, but no differences were found between the subgroups for this period. Subgroups based on changes in FEV_1 differed only with respect to change in peak oxygen uptake the first year after discharge.

Conclusions: In our study, many persons with SCI showed a decline in PF, larger than the normal age-related decline, during the 5 years after inpatient rehabilitation. Results suggest that a decline in PF during the first year after inpatient rehabilitation is associated with higher body mass index, lower inspiratory muscle strength, and declined physical fitness.

INTRODUCTION

Persons with a spinal cord injury (SCI) have a decreased life expectancy and an increased risk of medical complications as compared with able-bodied persons.[1, 2] Associations found in previous SCI studies, between low pulmonary function (PF) on the one hand and higher risk of respiratory illnesses[3, 4] and higher mortality rate[5] on the other hand, imply that PF might play an important role in these. Therefore, optimizing PF in the (sub)acute phase and preventing excessive decline in the chronic phase should be an important goal in SCI management.

PF is substantially reduced immediately after the onset of SCI but (partly) restores in the months thereafter.[6-8] Haisma et al[9] showed that PF improved still slightly during the first year after inpatient rehabilitation. In addition, results of cross-sectional studies suggested that PF declines faster in persons with chronic SCI than in able-bodied persons.[10, 11] Together, these findings suggest that at some point after onset, the initial improvement turns into a decline that surpasses the normal age-related decline. It is unclear when this alteration in course takes place. Therefore, it is important to follow the same cohort of persons for a longer period of time.

Not only is it unknown which changes take place in the long term, but it is also unknown whether excessive decline is predictable or preventable. In able-bodied persons, there is some evidence that lifestyle factors such as smoking, weight gain, physical fitness, and physical activity level are related to changes in PF over time.[12-16] In chronic SCI, negative associations with smoking and weight gain were found,[17] but associations with physical fitness and activity level have not been studied. Because many persons with SCI have difficulty maintaining a healthy and active lifestyle after inpatient rehabilitation,[18, 19] we hypothesized that persons with SCI are vulnerable to excessive decline in PF in the early years after rehabilitation and that lifestyle factors play a role in these.

The aim of our study was to describe changes in PF during the first 5 years after inpatient rehabilitation. To determine whether decline is predictable or preventable, we studied whether subgroups with declined, stable, or improved PF after inpatient rehabilitation differed from each other in modifiable factors such as smoking, inspiratory muscle strength, body mass index (BMI), physical fitness, and physical activity level.

METHODS

The present study was part of the Dutch research program "Physical strain, work capacity and mechanisms of restoration of mobility in the rehabilitation of persons with SCI",[20] in which 225 persons with recent SCI were included and measured for a variety of outcomes at several fixed test occasions during inpatient rehabilitation and 5 years thereafter. Persons were included in the program if they were: admitted for initial (i.e., not readmission) inpatient rehabilitation to 1 of 8 Dutch rehabilitation centers specialized in SCI rehabilitation between August 2000 and July 2003; had an SCI with American Spinal

Injury Association Impairment Scale (AIS) grade A, B, C, or D; were between 18 and 65 years of age; and were expected to remain wheelchair dependent. Persons with a progressive disease (such as a malignant tumor) or a psychiatric problem and those who did not sufficiently comprehend the Dutch language were excluded.[21] The research protocol was approved by the medical ethics committee of the SRL/iRv Hoensbroeck for the measurements up to 1 year after inpatient rehabilitation, and the medical ethics committee of the University Medical Center Utrecht approved the addition of the measurement 4 years thereafter. All participants gave written informed consent. The present study was a continuation of the studies of Haisma[9] and Mueller[22] and colleagues; they studied the course of PF up to 1 year after rehabilitation using part of the same data.

Participants

Four test occasions from the Dutch research program were relevant for the present study: the start of active rehabilitation (defined as the moment when a person was able to sit for 3-4 consecutive hours), discharge from the inpatient setting, and 1 and 5 years after discharge. We included persons whose PF was determined at 2 or more of these test occasions. PF was not determined in persons with mechanical ventilation or tracheostomy.

Pulmonary function

To determine PF, participants performed PF tests with an Oxycon Delta[a] seated in their wheelchair. Three repeated forced flow volume curves were made. In case of a non-characteristic curve, an extra measurement was performed.[23] The best trial, that is, the trial with the highest sum of the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), was used for further analyses. FVC and FEV_1 were expressed as a percentage of the predicted values based on able-bodied persons of the same age, gender, and height. Change in percent-predicted FVC and FEV_1 (value at endpoint minus value at baseline) was calculated for the period between discharge and 1 year thereafter and for the period between 1 and 5 years after discharge. This outcome was used to categorize persons into 3 subgroups: persons with (1) declined (change≤−5%), (2) stable (−5%<change<+5%), or (3) improved (change≥+5%) PF.

Lesion characteristics

Level and completeness of the lesion were determined by a physician according to the International Standards for Neurological and Functional Classification of Spinal Cord Injury.[24] Tetraplegia was defined by (partial) loss of motor function at or above the first thoracic level. Paraplegia was defined as (partial) loss of motor function below the first thoracic level. The lesion was defined as complete if there was no motor function in the lowest sacral segment (AIS A or B), and as incomplete if motor function was present (AIS C or D). Following this classification, participants were categorized in 4 different lesion groups: complete tetraplegia, incomplete tetraplegia, complete paraplegia, and incomplete paraplegia.

Modifiable factors

Smoking status (current smoker vs nonsmoker), BMI (body mass divided by height squared in kg/m^2), and physical fitness were assessed at all test occasions if possible.

Inspiratory muscle strength was determined at discharge and 1 year thereafter by measuring the maximal inspiratory pressure (MIP) at the mouth that could be maintained for 1 second.[22] Persons were tested in the seated position wearing a nose clip and breathing through a calibrated respiratory threshold meter[b] connected to a computer. They were instructed to breathe out maximally and then breathe in through the mouthpiece with maximal force. Measurements were performed until 3 reproducible measurements within at least 5% were registered; the best value was used for analyses.

Physical fitness was assessed with a maximal wheelchair-test as described by Kilkens et al.[25] Persons propelled a manual wheelchair on a motor-driven treadmill with constant velocity while the the inclination was increased every minute up to exhaustion. Peak power output (PO$_{peak}$) was defined as the power output at the highest inclination that could be maintained for at least 30 seconds, and peak oxygen consumption (VO$_{2peak}$) was defined as the highest oxygen consumption recorded during 30 seconds.

Physical activity level was determined 1 and 5 years after discharge by the Dutch version of the Physical Activity Scale for Individuals with Physical Disabilities.[26] This questionnaire records the number of days per week and the hours per day for participation in leisure time, household, and occupational physical activities over the past 7 days. A total physical activity score was calculated by multiplying the average hours per day for each item by a metabolic equivalent value (MET) associated with the intensity of the activity and summed over items resulting into a score between 0 (lowest level of activity) and 182.3 (highest level of activity) MET per hours per day (MET h/d).[27]

Statistical analyses

To detect selection bias, participants were compared with the participants of the Dutch research program who were excluded for our study, using independent Student t tests for the continuous variables and the Phi-Cramers'V tests for nominal variables.

Random coefficient analysis (MLwinN^c) was used to study overall changes in PF during inpatient rehabilitation and the 5 years thereafter.[28] Forced vital capacity and FEV$_1$ were the dependent variables and time was the independent variable entered as dummy variables for the test occasions. The test occasions at discharge and 5 years after were used as reference. Next, lesion groups were added to the basic models as dummy variables with the complete tetraplegia group as the reference. Finally, differences in changes in FVC and FEV$_1$ over time between lesion groups were determined by entering time, lesion groups, and the interactions between time and lesion groups as independent variables.

To study changes in PF after inpatient rehabilitation in more detail, we determined the percentages of persons with 'declined', 'stable', or 'improved' PF in the period between discharge and 1 year after and the period between 1 and 5 years after discharge. We tested whether these 3 subgroups differed for

the following determinants: age, sex, lesion characteristics, smoking status, and (change in) MIP, BMI, PO_{peak}, VO_{2peak}, and physical activity level. This was done with 1-way analysis of variance for means (SD), chi-square tests for proportions, or Kruskal-Wallis tests for medians (interquartile range). Values determined at the start of each period were used in these analyses. For physical activity level, we used values determined at the end of each period because this variable was not determined at discharge. Change in smoking status was negligible and therefore disregarded. Descriptive and comparative analyses were performed with SPSS 17.0[d]; significance was set at $P<0.05$.

RESULTS

Participants

In the present study, 180 persons were included; their characteristics are presented in Table 1. Forty-five persons from the Dutch research program were excluded because PF was not determined at 2 or more test occasions. These excluded persons were on average 5 years older than our participants, but did not differ with respect to lesion level or completeness, duration of inpatient rehabilitation, sex, smoking status prior to the SCI, and FVC at the start of active rehabilitation.

Table 1: Participants' characteristics (N=180)

Age at the start of active rehabilitation* (years)	39.7 ± 13.7
Time since injury at the start of active rehabilitation* (days)	101.8 ± 62.1
Duration inpatient rehabilitation (days)	274.7 ± 152.0
Smoking status prior to SCI, smokers	43.5
FVC at the start of active rehabilitation* (% predicted)	71.8 ± 25.1
Sex, men	73.9
Lesion level, tetraplegia	38.9
Completeness, motor complete (AIS A and B)	66.7
Complete lesions (AIS A and B)	
C3-C5 (n=17)	9.4
C6-C8 (n=24)	13.3
T1-T6 (n=30)	16.7
T7 and below (n=49)	27.2
Incomplete lesions (AIS C and D)	
C3-C5 (n=14)	7.8
C6-C8 (n=15)	8.3
T1-T6 (n=5)	2.8
T7 and below (n=26)	14.4

NOTE. Values are mean ± SD, %, or as otherwise indicated. *The start of active rehabilitation was defined as the moment when a person was able to sit for 3-4 consecutive hours
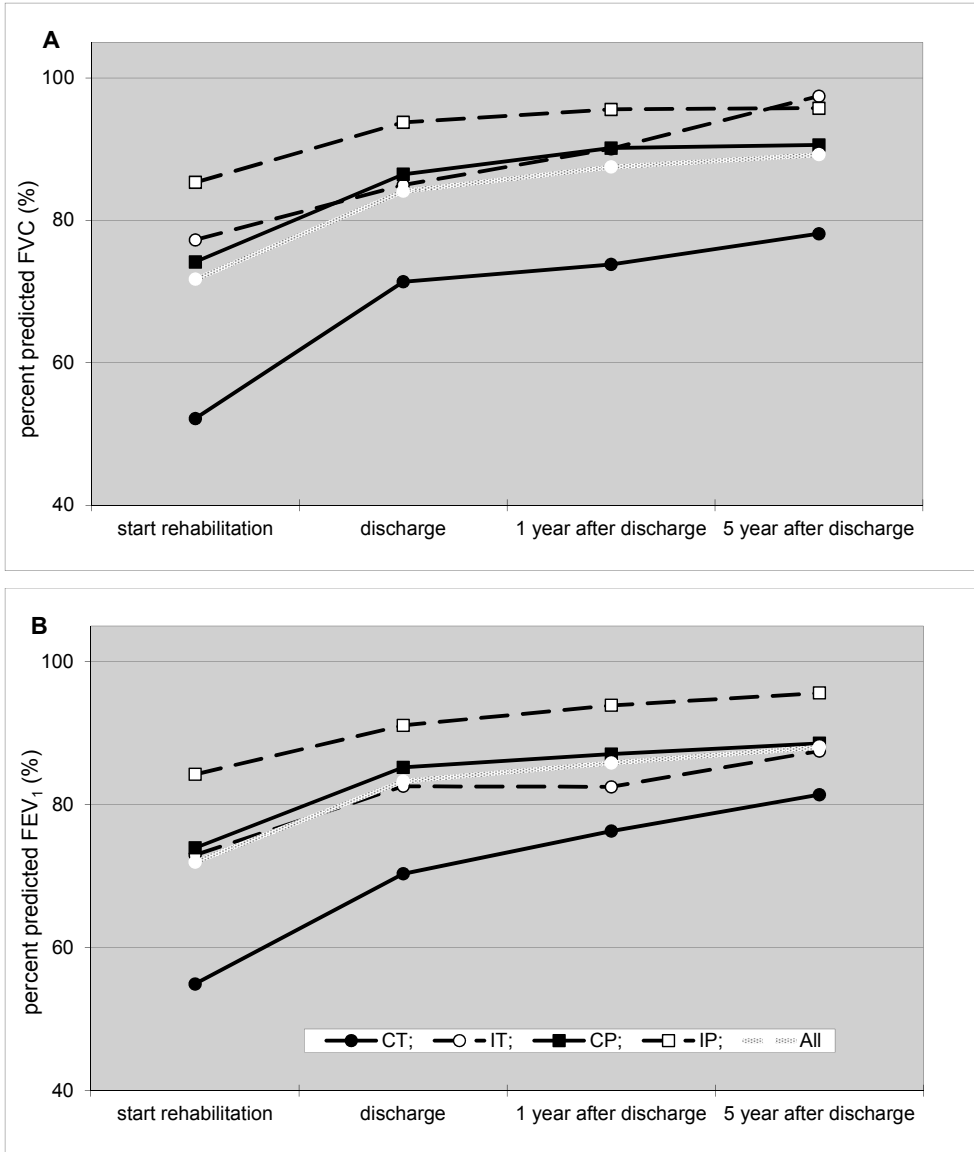
Figure 1. Overall changes in pulmonary function during inpatient rehabilitation and the 5 years thereafter. Calculated estimates from the basic multilevel regression model (white line, n=180) and the final multilevel regression model (black lines) for changes in (A) FVC, and (B) FEV1 expressed in percentage of the predicted values based on able-bodied persons of the same age, sex, and height for 4 different lesion groups. Abbreviations: CP=complete paraplegia (n=79); CT=complete tetraplegia (n=41, reference group); IP=incomplete paraplegia (n=31); IT=incomplete tetraplegia (n=29).

Overall changes in pulmonary function

PF improved overall on average 12.4% (from 71.7% to 84.1%) predicted FVC (confidence interval (CI), 9.9 to 14.9) and 11.3% (from 72.0% to 83.3%) predicted FEV_1 (CI, 8.9 to 13.7) during inpatient rehabilitation (Figure 1A and B, white line). Between discharge from inpatient rehabilitation and 5 years thereafter, FVC improved on average another 5.1% (from 84.1% to 89.2%) over the whole period (CI, 0.0 to 10.2). No change was found for FEV_1 (CI, –0.1 to 9.7). Examining changes over the 2 separate periods after inpatient rehabilitation (first year after discharge and between 1 and 5 years after discharge) did not reveal any change.

Persons with complete tetraplegia had significantly lower PF than persons with incomplete tetraplegia, complete paraplegia, or incomplete paraplegia ($P<.001$) (Figure 1A and B, black lines). Their change in PF in the period after discharge was not different than that in other lesion groups.

Subgroups with declined, stable, or improved pulmonary function

In persons tested at discharge as well as 1 year thereafter, the change in FVC ranged from –23.3% to +31.6% and the SD from the mean was 8.5%. During this first year after discharge, FVC declined in 14.9%, stabilized in 43.8%, and improved in 41.3% of our population. In persons tested 1 as well as 5 years after discharge, the change in FVC ranged from –22.6% to 26.6% and the SD was 8.8%. During these 4 years, FVC declined in 28.3%, stabilized in 40.2%, and improved in 31.5% (Figure 2). For FEV_1 similar ranges, SDs, and percentages were found.
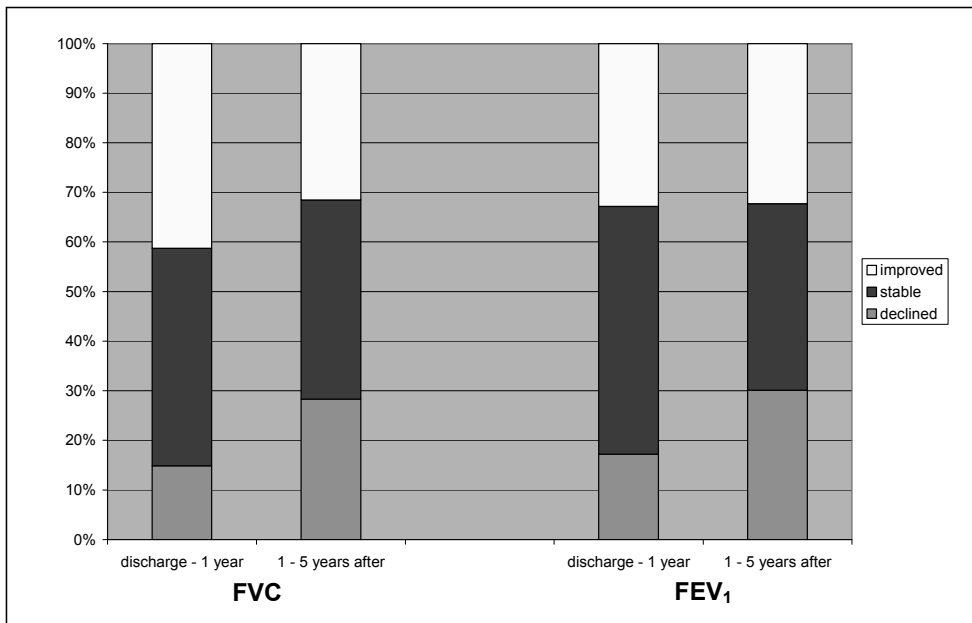
Figure 2. Percentage of persons with declined, stable, or improved FVC and declined, stable, or improved FEV1 between discharge of inpatient rehabilitation and 1 year thereafter and between 1 and 5 years after discharge.

For FVC, we found statistically significant differences between subgroups in BMI, MIP, change in PO_{peak}, and change in VO_{2peak} for the first year after discharge. Those who declined showed highest BMI, lowest MIP, a negative change in PO_{peak}, and a negative change in VO_{2peak} (Table 2). For FEV_1, we found only significant differences in change in VO_{2peak} for the first year after discharge with a negative change for those that declined (Table 3). For the 4 years thereafter, no statistically significant differences were found between subgroups.

DISCUSSION

To the best of our knowledge, the present study was the first to describe changes in PF after SCI during the 5 years after inpatient rehabilitation and to study potential determinants of changes during this time period.

Overall changes in pulmonary function

In agreement with previous findings,[11, 29] PF was more impaired in persons with more severe neurological deficits. Five years after discharge, persons with complete tetraplegia had a PF of approximately 80% of the predicted value, while persons with other lesion groups approached the norm value for able-bodied persons. The mean values we found were higher than reported in other studies, which might be caused not only by differences in population (younger age and shorter time since injury), but also by a difference in treatment regimen. The duration of rehabilitation tends to be longer in the Netherlands than in many other countries.[30] Therefore, participants in our study may have had a better chance to optimize their PF before leaving the rehabilitation center.

Although absolute levels of PF differed between lesion groups, changes in PF in the period after rehabilitation did not. This finding is in agreement with the results of Stolzmann et al[17] and suggests that, in contrast to what is often assumed in clinical practice, the risk of excessive PF decline is not limited to persons with tetraplegia, but also occurs in those with less severe injury.

Subgroups with declined, stable, or improved pulmonary function

We found large interpersonal differences in change in PF during the first 5 years after inpatient rehabilitation. In many, PF improved in these years while in others PF declined. A considerable number of persons saw their PF decline with more than 5% (adjusted for age-related decline) in the 5 years after discharge. These results suggest that some persons might still have potential for further recovery after rehabilitation while others are not even able to maintain the acquired function. Because previous studies have demonstrated that for each lower percent-predicted FVC or FEV_1 the mortality rate in SCI increases by 3%, these are alarming high percentages.[5] Therefore, it seems important to allocate those at risk of a decrease in PF.

The results of the present study suggest that unfavorable BMI, MIP, change in PO_{peak}, and change in VO_{2peak} are associated with a decline in PF in the first year after inpatient rehabilitation. The sugges-

Table 2. Differences between subgroups with declined, stable, or improved forced vital capacity (FVC)

Determinants	Discharge to 1 year after					1 – 5 years after discharge				
	n	Declined	Stable	Improved	P	n	Declined	Stable	Improved	P
n (%)	121	18 (14.9)	53 (43.8)	50 (41.3)	NA	92	26 (28.3)	37 (40.2)	29 (31.5)	NA
Age (y)	121	42.7 ± 13.9	38.4 ± 13.6	38.3 ± 13.5	.462	92	44.3 ± 14.1	37.4 ± 12.3	38.0 ± 13.5	.111
Sex, men	121	77.8	64.2	82.0	.110	92	84.6	73.0	69.0	.382
Lesion level, tetraplegia	121	38.9	32.1	40.0	.685	92	34.6	24.3	41.4	.330
Completeness of lesion, motor complete	121	72.2	69.8	74.0	.894	92	76.9	73.0	69.0	.803
Smoking status, current smokers	120	27.8	30.8	38.0	.640	91	34.6	27.1	27.6	.784
BMI (kg/m^2)	119	25.0 ± 3.4	22.5 ± 3.6	23.4 ± 3.9	**.042**	92	25.0 ± 4.2	25.3 ± 4.9	22.8 ± 3.7	.064
Change in BMI (kg/m^2)	117	1.2 ± 2.0	0.9 ± 1.5	1.3 ± 2.2	.667	91	2.0 ± 2.2	1.0 ± 3.3	0.7 ± 1.8	.179
MIP (cm H$_2$O)	48	34.6 ± 17.0	71.7 ± 27.9	72.3 ± 35.0	**.027**	31	84.7 ± 28.2	80.8 ± 33.0	68.3 ± 26.5	.442
Change in MIP (cm H$_2$O)	29	-1.4 ± 20.2	0.0 ± 20.7	11.6 ± 22.2	.340	NA	NT	NT	NT	NA
POpeak (W)	93	39.0 ± 23.8	45.6 ± 26.8	42.2 ± 17.9	.605	67	48.6 ± 24.5	50.0 ± 25.1	44.6 ± 29.6	.779
Change in POpeak (W)	78	-5.2 ± 12.1	2.6 ± 10.8	6.4 ± 10.4	**.011**	48	-4.5 ± 13.9	5.1 ± 12.3	2.8 ± 9.3	.094
VO2peak (ml/min)	91	1170.0 ± 363.0	1258.4 ± 554.0	1211.4 ± 369.3	.802	66	1308.3 ± 526.3	1345.8 ± 416.4	1348.9 ± 780.1	.969
Change in VO2peak (ml/min)	75	-108.3 ± 271.2	64.9 ± 240.8	173.6 ± 232.5	**.006**	48	-7.3 ± 269.7	138.4 ± 350.2	30.6 ± 291.8	.396
PASIPD score (MET h/d)	110	12.0 (3.1-47.5)	19.5 (5.7-32.3)	8.8 (3.8-18.4)	.189	81	10.7 (4.9-20.8)	16.3 (10.3-33.6)	16.0 (5.9-39.9)	.144
Change PASIPD	NA	NT	NT	NT	NA	76	2.4 ± 12.2	5.1 ± 17.4	-0.2 ± 18.9	.511

NOTES. Values are means ± SD, %, or as otherwise indicated. Differences between subgroups were tested with 1-way ANOVA for means ± SD, chi-square tests for proportions, or Kruskal-Wallis tests for medians (IQR). Abbreviations: NA=not applicable; NT=not tested; IQR=interquartile range. P-values<.05 are highlighted in boldface font.

Table 3. Differences between subgroups with declined, stable, or improved forced expiratory volume in 1 second (FEV1)

Determinants	n	Discharge to 1 year after				n	1 – 5 years after discharge			
		Declined	Stable	Improved	P		Declined	Stable	Improved	P
n (%)	122	21 (17.2)	61 (50.0)	40 (32.8)	NA	93	28 (30.1)	35 (37.6)	30 (32.3)	NA
Age (y)	122	41.0 ± 14.0	39.1 ± 14.0	37.5 ± 13.0	.638	93	42.7 ± 13.6	39.5 ± 13.2	36.7 ± 12.9	.257
Sex, men	122	76.2	73.8	72.5	.953	93	75.0	74.3	76.7	.975
Lesion level, tetraplegia	122	38.1	31.1	42.5	.498	93	25.0	28.6	46.7	.163
Completeness of lesion, motor complete	122	81.0	67.2	75.0	.425	93	82.1	68.6	66.7	.357
Smoking status, current smokers	121	23.8	36.7	35.0	.554	93	39.3	20.0	30.0	.243
BMI (kg/m^2)	120	24.6 ± 3.2	22.5 ± 3.5	23.6 ± 4.1	.054	93	24.6 ± 4.0	25.0 ± 5.3	24.0 ± 4.1	.691
Change in BMI (kg/m^2)	118	0.9 ± 1.8	1.1 ± 1.7	1.3 ± 2.2	.756	92	2.0 ± 2.7	1.1 ± 2.9	1.0 ± 2.5	.092
MIP (cm H$_2$O)	48	55.7 ± 33.1	74.7 ± 28.8	64.6 ± 35.9	.313	32	81.9 ± 34.2	85.5 ± 25.5	66.2 ± 28.2	.226
Change in MIP (cm H$_2$O)	29	8.9 ± 18.1	10.8 ± 16.6	12.6 ± 22.0	.380	NA	NT	NT	NT	NA
POpeak (W)	94	42.2 ± 22.2	45.2 ± 24.0	41.3 ± 23.6	.764	68	41.7 ± 23.3	56.1 ± 25.8	42.9 ± 27.5	.106
Change in POpeak (W)	79	–3.2 ± 12.8	3.3 ± 10.3	3.5 ± 12.9	.162	48	–1.1 ± 14.0	2.4 ± 12.2	4.3 ± 9.9	.489
VO2peak (ml/min)	92	1216.2 ± 363.3	1245.3 ± 499.6	1208.1 ± 455.2	.940	67	1283.1 ± 587.1	1441.2 ± 491.7	1281.9 ± 603.7	.535
Change in VO2peak (ml/min)	76	–68.5 ± 281.8	51.6 ± 245.4	182.7 ± 238.8	**.017**	47	27.6 ± 327.7	110.6 ± 283.1	50.7 ± 341.4	.741
PASIPD score (MET h/d)	110	12.0 (3.9-44.9)	13.7 (4.0-28.1)	10.3 (4.4-22.1)	.723	82	14.9 (6.2-38.9)	13.9 (6.6-28.6)	16.1 (6.5-28.7)	.993
Change PASIPD	NA	NT	NT	NT	NA	77	5.9 ± 18.6	1.9 ± 13.8	1.2 ± 17.9	.571

NOTES. Values are means ± SD, %, or as otherwise indicated. Differences between subgroups were tested with 1-way ANOVA for means ± SD, chi-square tests for proportions, or Kruskal-Wallis tests for medians (IQR). Abbreviations: NA: not applicable; NT: not tested; IQR: interquartile range. P-values<.05 are highlighted in boldface font.

tion that a higher BMI has a negative association with change in PF is in agreement with findings in able-bodied persons and in persons with chronic SCI.[13, 17] It suggests that control of body weight may contribute to a good PF. In addition, the positive association between MIP and change in PF is in agreement with findings in persons with chronic SCI.[17] In our study, the subgroup with declined PF had an MIP below the lower limit of normal in able-bodied persons, indicating clinically important weakness of inspiratory muscles.[31] Therefore, training inspiratory muscle strength, for example, through respiratory training exercises may enhance PF. PO_{peak} (maximal maintainable workload) and VO_{2peak} (aerobic capacity) measure physical fitness. Physical fitness is generally assumed, but not previously proven, to have positive effects on PF.[12, 32] Our results showed that persons with declined PF suffered, on average, from decline in fitness whereas persons with stable or improved PF showed improvement in fitness. In our opinion, decline in physical fitness is more than simply a marker of decline in PF, because physical fitness is dependent on the combined capacity of the cardiovascular, musculoskeletal, and respiratory systems. Therefore, finding means to prevent decline in physical fitness after inpatient rehabilitation may play a positive role in the prevention of decline in PF.

We found no differences in physical activity level between subgroups. Perhaps, the activity levels in the majority of this population are just not high enough to cause any effect on PF. Furthermore, the Physical Activity Scale for Individuals with Physical Disabilities might not measure the specific aspect of activity that influences PF. Other aspects of physical activity, for instance, short episodes of high intensive movement, might be of more interest in this respect.

Surprisingly, there were no differences in smoking status between subgroups. It is a well-established fact that smoking accelerates decline of PF in able-bodied persons.[12, 15] We do not think that the actual lung tissue responds differently to smoking in those with an SCI than in able-bodied persons. Possibly, injury-related functional loss has overshadowed the effect of smoking as suggested in previous studies.[33]

For the period between 1 and 5 years after discharge, there were no significant differences between subgroups. Nevertheless, for most determinants, similar patterns were found. The smaller number of participants for this period may have caused a lack of statistical power. Moreover, perhaps other (unknown) factors play a role in the more chronic phase after inpatient rehabilitation.

Clinical relevance

Our results may have identified means to prevent (or at least be aware of the risk of) excessive decline of PF. Exercises to improve inspiratory muscle strength and adding treatment programs that aim at weight control and maintaining fitness after inpatient rehabilitation may be beneficial to prevent decline of PF and therewith decrease the risk of motility and mortality. However, it has to be realized that changes in PF differ largely between individuals and remain difficult to predict. Therefore, we strongly recommend monitoring PF in all persons with SCI after rehabilitation.

Study Limitations

Some limitations of our study have to be considered. The 45 excluded persons were significantly older than the participants. Because these were likely the more vulnerable persons (including the deceased), we may have underestimated the actual proportion of those showing a decline. In addition, not all persons included in our study performed all tests at all test occasions, therewith lowering statistical power in the second part of the study. Particularly, inspiratory muscle strength and physical fitness level were measured in a limited number of persons. In addition, physical fitness was not measured in persons depending on electrical powered wheelchairs (likely the ones with lowest capacity) which might have influenced the results. Finally, the descriptive character of this study does not allow us to draw conclusions on cause and effect.

CONCLUSIONS

Despite a small, on average, improvement at group level, a considerable proportion of persons with SCI showed a decline in PF, larger than the normal age-related decline, during the 5 years after inpatient rehabilitation. The results suggest that higher BMI, lower inspiratory muscle strength, and decline of physical fitness are associated with a decline in PF in the first year after inpatient rehabilitation. More information is needed on factors influencing PF in the more chronic phase after inpatient rehabilitation. Further research is necessary to confirm these results in a larger population and to evaluate the effectiveness of treatment programs that aim to prevent excessive decline of PF.

SUPPLIERS

a. CareFusion: Leibnizstrasse 7, 97204 Hoechberg, Germany.
b. Instrumental Department, Radboud University Nijmegen, P.O. Box 9102, 6500 HC Nijmegen, the Netherlands.
c. Centre for Multilevel Modeling, University of Bristol, 2 Priory Road, Bristol BS8 1TX, UK.
d. SPSS, Inc. 233 S Wacker Dr, 11th FL, Chicago, IL 60606, USA.

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Chapter 4

Impaired respiratory function and associations with health-related quality of life in persons with spinal cord injury

Karin Postma
Marcel W.M. Post
Janneke A. Haisma
Henk J. Stam
Michael P. Bergen
Johannes B.J. Bussmann

ABSTRACT

Objectives: to examine the prevalence of impaired respiratory function, the incidence of respiratory infection, and the associations among these parameters in persons with spinal cord injury (SCI) 5 years after initial inpatient rehabilitation. Secondly we assessed associations between respiratory function and health-related quality of life (HRQOL).

Design: Follow-up measurement in a multicenter prospective cohort study

Subjects: 147 persons with SCI

Methods: Measurements were performed 5 years after discharge from inpatient rehabilitation. Objectively measured respiratory function was determined by forced vital capacity (FVC) and perceived respiratory function by self-reported cough strength and dyspnea. Respiratory infection was determined by a physician. Four domains of HRQOL domains were measured using the Sickness Impact Profile 68 and the 36-item Short Form Health Survey.

Results: Of this sample 30.9% had impaired FVC, 35.9% impaired cough strength, 18.4% dyspnea at rest, and 29.0% dyspnea during activity. In the year prior to the measurements 8.9% had had respiratory infection. Impaired FVC was associated with cough strength but not with dyspnea. All respiratory function parameters were associated with social functioning, while other HRQOL-domains were associated with dyspnea only.

Conclusion: Five years after initial inpatient rehabilitation impaired respiratory function and respiratory infection was common in persons with SCI. More severely impaired respiratory function was associated with lower HRQOL.

INTRODUCTION

Injury of the spinal cord affects the respiratory muscles resulting in impaired respiratory function includ-ing low pulmonary function, weak cough strength, and difficulty in breathing. The higher and more complete the injury, the more respiratory muscles are affected and the more respiratory function may be impaired.[1] In the early phase after injury, respiratory care is an essential part of medical and rehabilita-tion management, but respiratory care in the chronic phase may not be optimal.[2] After all, respiratory complications such as respiratory infections, continue to be an important cause of hospitalization and early death in persons with chronic spinal cord injury (SCI) after the first year post-onset.[3, 4]

Previous studies showed impaired pulmonary function and cough strength in persons with chronic SCI.[1, 5] Additionally, several studies have demonstrated that a sensation of breathlessness (dyspnea) is com-mon (between 6 and 68% depending on the group studied) in persons with chronic SCI.[6-8] However, most of these studies focused on one aspect of respiratory function or respiratory infection only, and included persons with a variable and long mean time after injury (longer than 10 years). Therefore, little is known about the effects of SCI in the early years after initial rehabilitation and about relationships between different aspects of respiratory function and their relationships with respiratory infection.

Respiratory function is not only relevant in itself and in association with respiratory infection, but im-paired respiratory function may also affect one's health-related quality of life (HRQOL, including physical, mental and social aspects).[9] However, so far knowledge on this topic is scarce and results are inconsis-tent. Jain et al[10] found significant associations between several respiratory symptoms and functioning (physical and social limitations), mood state, and global quality of life; Jensen et al[7] found significant associations between dyspnea and fatigue, but not between dyspnea and social integration or mental functioning. In addition, an association between pulmonary function and functioning, but not between pulmonary function and mood state or global quality of life, was found.[10]

Following the above, the aim of the present study was to examine the prevalence of impaired objectively measured respiratory function (pulmonary function), perceived respiratory function (cough strength and dyspnea), the incidence of respiratory infection, and the associations among these parameters in persons with SCI 5 years after initial inpatient rehabilitation. The second aim was to assess the associa-tions between respiratory function and HRQOL (expressed as: social functioning, general health, mental health and vitality).

METHODS

Participants

For the present study we used data of the 5-year follow-up measurement of the Dutch multicenter prospective cohort study "restoration of mobility in spinal cord injury".[11] The original cohort counted 225

participants at the first test occasion (start of initial inpatient rehabilitation) and inclusion criteria were: a recent SCI, admission to one of the 8 participating rehabilitation centers with specialized SCI units in the Netherlands from August 2000 to July 2003, between 18 and 65 years of age, grade A, B, C, or D on the American Spinal Injury Association Impairment Scale (AIS), and expected (partial) wheelchair-dependency. Exclusion criteria were: a progressive disease, a psychiatric condition, or insufficient comprehension of the Dutch language. The follow-up measurement 5 years after inpatient rehabilitation was approved by the medical ethics committee of the University Medical Centre Utrecht. All participants gave written informed consent.

Procedure

Persons included in the original cohort study were contacted and invited for this follow-up study 5 years after discharge from inpatient rehabilitation. Measurements used in the current study included an examination by a rehabilitation physician, a pulmonary function test by a trained research assistant, an oral interview and a mailed questionnaire.

Respiratory function

Both objectively measured respiratory function and perceived respiratory function were assessed. Objectively measured respiratory function was measured with a pulmonary function test using the Oxycon Delta[a]. Forced vital capacity (FVC) expressed as percentage of the predicted value based on able-bodied persons of the same age, sex, and height was used as outcome measure. Persons were tested seated in their wheelchair and wearing a nose clip. Three repeated forced flow volume curves were made. In case of a non-characteristic curve, an extra measurement was performed.[12] The trial with the highest sum of the FVC and forced expiratory volume in one second was used for further analyses.

Perceived respiratory function was expressed by self-reported cough strength and dyspnea. By means of a mailed questionnaire persons were asked to rate their cough strength in the seated position as: poor, moderate, fairly strong, or strong. Next, they were asked how often they experienced breathlessness in rest and during physical activity: never or rarely, occasionally, regularly, or often.

Parameters of respiratory function were divided into 3 impairment severity categories. Forced vital capacity was considered not impaired if the percent predicted value was 80% or higher, mildly impaired if FVC was between 60% and 80%, and severely impaired if FVC was below 60%. Cough strength was considered not impaired if rated fairly strong or strong, mildly impaired if rated moderate, and severely impaired if rated poor. Dyspnea was considered a severe impairment if dyspnea was experienced regularly or often, a mild impairment if dyspnea was experienced occasionally, and no impairment if dyspnea was not present (breathlessness experienced never or rarely).

Respiratory infections

Whether persons had had respiratory infection during the year prior to the measurements was determined by a physician using a semi-structured interview on secondary complications. Physicians were

instructed to record only clinically important infections, not simple nose or head colds, as respiratory infection.

Health-related quality of life

Four domains of HRQOL were measured. Social Functioning was measured with the social dimension of the Sickness Impact Profile 68 (SIPSOC), which is the sum-score of the subscales Mobility Range and Social Behavior.[13] The score range is 0 to 22; high scores reflect more limitations in social functioning. Furthermore, perceived General Health, Mental Health (psychological functioning) and Vitality (energy and fatigue) were measured with the corresponding subscales of the 36-item Short Form Health Survey questionnaire (SF-36).[14] The score range in each subscale was 0 (lowest) to 100 (highest). High scores reflect good general health, mental health and vitality. The Sickness Impact Profile 68 and SF-36 proved to be reliable and valid in persons with SCI.[13, 15, 16]

Other variables

Lesion characteristics were determined according to the International Standards for Neurological and Functional Classification of Spinal Cord Injury.[17] Persons were classified by lesion level: tetraplegia or paraplegia, and completeness of lesion: motor complete (AIS A or B) or incomplete (AIS C or D). In addition, the presence of concomitant respiratory conditions was scored if the physician had reported that the person suffered from a respiratory disease other than respiratory infection in the year prior to the measurement (i.e. asthma, COPD, or pulmonary embolism) or if data from previous measurements showed that the person had a condition prior to or at the onset of SCI that was likely to affect pulmonary function largely (lobectomy, echinococcus in the lung tissue, and M. Bechterew).

Statistical analyses

A non-response analysis was performed by comparing baseline characteristics of participants of the present study with participants of the original cohort who did not complete the measurements 5 years after inpatient rehabilitation, by using independent Student t tests for continues variables and Phi-Cramers'V tests for nominal variables.

Descriptive statistics was used to calculate the prevalence of impaired respiratory function and the incidence of respiratory infection. Associations between FVC and perceived respiratory function, and between FVC and respiratory infection were assessed by comparing the distribution of FVC across different impairment severity categories for cough strength and dyspnea and between groups with and without respiratory infection using the Kruskal-Wallis tests.

Linear regression analysis was used to study associations between respiratory function and HRQOL. Dependent variables were the different domains of HRQOL. Independent variables were the parameters of respiratory function: FVC, cough strength, dyspnea at rest and dyspnea during activity. For cough strength, poor and moderate cough strength were entered as dummy variables (fairly strong or strong was used as reference). For dyspnea the categories regularly or often and occasionally were entered as

dummies (never or rarely was used as reference). To correct for SCI characteristics, lesion level (tetraplegia or paraplegia) and lesion completeness (motor complete or incomplete) were included as independent variables in this analysis first. For all analyses the significance level was set at 0.05.

RESULTS

One-hundred forty-seven persons with SCI participated in the Dutch multicenter prospective cohort study 5 years after inpatient rehabilitation. Their characteristics are presented in Table 1. All persons breathed without mechanical support and were without tracheotomy. Nine persons had concomitant conditions: COPD (4), asthma (1), status after lobectomy due to lung cancer (2), echinococcus in the lung tissue (1), and M. Bechterew (1). One person had had a pulmonary embolism within the year prior to the measurement. Participants of the present study did not significantly differ from participants of the original cohort who did not complete the measurements 5 years after inpatient rehabilitation (the non-participants, n=78) concerning sex, lesion level, and completeness of lesion. However, the participants were on average younger than the non-participants (mean age 39.2 years versus 43.4 years old; P=.04) and in this group the cause of SCI was more often traumatic (78.9 versus 63.6%; P=.01).

Table 1: Demographic characteristics (N=147)

Age (years), mean ± SD	45.5 ± 13.8
Sex, % men	71.4
Lesion group, n (%)	
Complete tetraplegia	33 (22.4)
Incomplete tetraplegia	21 (14.3)
Complete paraplegia	67 (45.6)
Incomplete paraplegia	26 (17.7)
Cause of injury, % traumatic	78.9
Time since injury (years), mean ± SD	6.6 ± 0.8
Smoking status, % current smokers	23.2

Table 2 shows that 30.9% of all persons had impaired FVC (below 80% of the predicted value), 35.9% perceived impaired cough strength (poor or moderate), and 18.4% (at rest) and 29.0% (during activity) experienced dyspnea (occasionally or regularly). During the year prior to the measurements 12 persons had had respiratory infection, of whom 7 had been confined to bed for at least one day and 5 had been hospitalized (unknown, 7, 7, 8, 21 days).
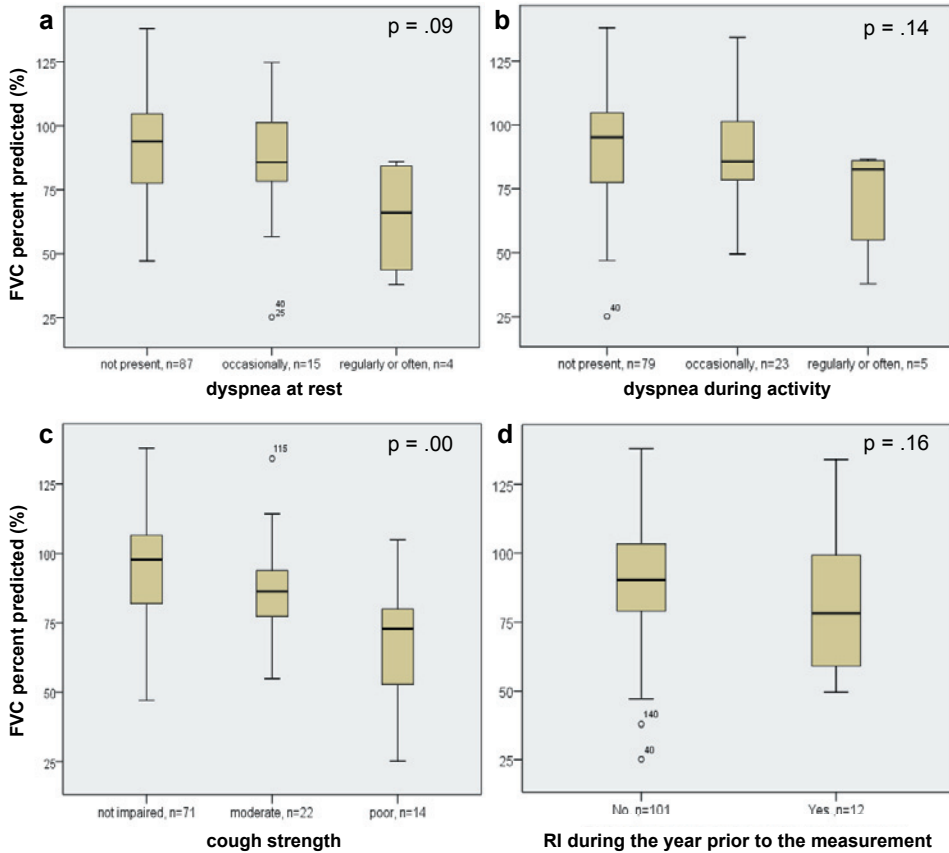
The distribution of FVC differed between impairment severity categories for cough strength; not impaired: median (IQR) 4.6 l/sec (3.6-5.4), moderate: 3.7 l/sec (2.8-4.3), weak: 2.7 l/sec (2.1-3.9), P=.00 (Figure 1). No significant difference was found between dyspnea categories and between persons with and without respiratory infection.

Associations between parameters of respiratory function and domains of HRQOL are presented in Table 3. When correction for lesion level and completeness, more limitations in social functioning were reported by persons with lower FVC, and persons who had severely impaired perceived cough strength and severe dyspnea. In addition, persons with dyspnea reported lower general health, mental health and vitality. Parameters of respiratory function contributed 2% to 6% of the explained variance of HRQOL.

Table 2: Prevalence of impaired respiratory function and incidence of respiratory infections for the whole study-group and per lesion group (CT: motor complete tetraplegia, IT: incomplete tetraplegia, CP: complete paraplegia, IP: incomplete paraplegia)

	All (n=147)	CT (n=33)	IT (n=21)	CP (n=67)	IP (n=26)
Percent predicted FVC, mean (SD)	89.8±20.5	76.9±16.7	96.7±23.6	91.1±18.5	96.9±22.0
FVC (n=113)					
Not impaired (≥80.0% predicted FVC)	78 (69.0)	12[1]*	9[1]	41[2]	16
Impaired					
Mild (60-80% predicted FVC)	25 (22.1)	8[1]	3	11[2]	3
Severe (<60% predicted FVC)	10 (8.8)	4	1	3	2[2]
Cough strength (n=139)					
Not impaired	89 (34.1)	12	8[1]	45[4]	24
Impaired					
Moderate	28 (20.1)	10[1]	4	14	0
Poor	22 (15.8)	10[1]	6	5[1]	1[1]
Dyspnea at rest (n=136)					
Not present	111 (81.6)	22[1]	15[1]	15[1]	23[1]
Present					
Occasionally	21 (15.4)	9	2	9[2]	1
Regularly or often	4 (3.0)	1[1]	0	2	1
Dyspnea during physical activity (n=138)					
Not present	98 (71.0)	24[1]	12[1]	43[3]	19[1]
Present					
Occasionally	33 (23.9)	7[1]	5	17[1]	4
Regularly or often	7 (5.1)	1	1	3[2]	2
Respiratory infection in the year prior (n=135)					
No	123 (91.1)	28[2]	15[1]	57[5]	23
Yes	12 (8.9)	4	2	5	1[1]

Note: For percent predicted FVC means (SD) are presented. All other values are number of persons (%). *The number of persons with concomitant respiratory illnesses (asthma, COPD and a status after lobectomy) in each lesion group are presented within brackets. Abbreviations: FVC=forced vital capacity.

Figure 1. Distribution of forced vital capacity (FVC) across different impairment severity categories for dyspnea at rest (a), dyspnea during activity (b), cough strength (c), and between groups with and without respiratory infection (d). Boxplots present median score (-), interquartile range (grey), minimum and maximum range (whiskers).

DISCUSSION

The present study showed that impaired respiratory function and respiratory infection was common in persons 5 years after inpatient rehabilitation for SCI. In addition, several associations between (impaired) respiratory function and domains of HRQOL were found.

Impaired respiratory function

The prevalence of impaired respiratory function was considerable in our study. However, more severe impairments were less common: only 8.8% of persons had severe impaired FVC (<60% predicted value), 15.8% gave their cough strength the lowest possible rating (poor), and few persons (3% in sit and 5% during activity) experienced dyspnea regularly or often. The prevalence rates of dyspnea found in our

study seemed in general lower than in previous studies.[6-8] Detailed comparison between studies was not possible due to differences in definitions of dyspnea, outcome measures and group compositions. Therefore, it is impossible to conclude whether prevalence rates in the early years after rehabilitation (our study population) are different from prevalence rates in long-standing SCI (over 10 year post onset). Nevertheless, similar to previous findings, our results showed that dyspnea at rest was more often present in persons with complete tetraplegia compared to other lesion groups, while dyspnea during activities was spread evenly over all lesion groups.[6, 8] The most likely explanation for this finding seems that the excess of functional loss, prevents persons with tetraplegia to be active in such a manner that the respiratory system is challenged.[18]

With exception of dyspnea during activity, impairments of respiratory function were more common in persons with more severe neurological injury (persons with complete tetraplegia). Nevertheless, impaired respiratory function was also prevalent in other lesion groups, even after disregarding persons with concomitant respiratory illnesses (asthma, COPD and a status after lobectomy). This suggests that respiratory care should not only focus on persons with high complete lesions, but also on others.

Table 3: Associations between respiratory function and domains of health-related quality of life (HRQOL), corrected for lesion level and completeness

	SIPSOC range: 0-22		General Health range: 0-100		Mental Health range: 0-100		Vitality range: 0-100	
Mean ± SD for all	6.7 ± 4.7		60.7 ± 23.3		77.5 ± 15.1		65.7 ± 16.2	
Variables	β±SE	P	β±SE	P	β±SE	P	β±SE	P
FVC,*								
10% predicted	−0.46 ± 0.22	.037	1.2 ± 1.1	.285	0.5 ± 0.8	.518	0.59 ± 0.8	.462
Cough strength,**								
Moderate	0.73 ± 1.01	.470	−4.7 ± 5.3	.374	−1.0 ± 3.5	.763	−2.0 ± 3.7	.600
Poor	3.37 ± 1.15	.004	−2.9 ± 6.1	.640	−5.2 ± 4.0	.193	−2.5 ± 4.4	.571
Dyspnea at rest,**								
Occasionally	1.60 ± 1.05	.131	−12.1 ± 5.5	.030	−1.1 ± 3.8	.772	−5.9 ± 4.1	.148
Regularly or often	6.82 ± 2.20	.002	−27.6 ± 11.5	.018	−16.0 ± 7.7	.040	−14.4 ± 8.2	.080
Dyspnea during physical activity,**								
Occasionally	1.33 ± 0.89	.136	−10.8 ± 4.6	.021	−8.4 ± 3.0	.007	−9.1 ± 3.3	.006
Regularly or often	5.38 ± 1.73	.002	−18.8 ± 8.9	.035	−12.7 ± 5.8	.030	−12.0 ± 6.1	.051

Note: *the regression coefficients (β) represent the change in outcome (HRQOL-score) associated with an increase in 10% predicted FVC; **the regression coefficients (β) represent the difference in outcome (HRQOL-score) between respectively moderate or poor cough strength and not impaired cough strength, and between respectively occasionally or regularly present dyspnea and no dyspnea. Abbreviations: SIPSOC=social dimension of the Sickness Impact Profile 68; SE=standard error; FVC=forced vital capacity.

Incidence of respiratory infection

The incidence of respiratory infection in the fifth year after inpatient rehabilitation (8.9%) was similar to that in the first year after rehabilitation in the same cohort[19] and to that reported in other chronic SCI populations.[3, 20, 21] The incidence found in the present study is considerably higher than in the general Dutch population (estimated incidence rate for lower tract respiratory infection was 2.9% in 2011).[22] Moreover, a relatively large part (5 out of 12) of persons were hospitalized due to respiratory infection.

Associations among parameters of respiratory function and respiratory infection

The lack of strong associations reflect the distinct constructs represented by the different respiratory function parameters, as well as differences in the way these were measured. For example, FVC is an objective measure, while cough strength and dyspnea were rated by self-report. Furthermore, FVC and cough strength are both measures of capacity, while dyspnea measures a perceived discomfort. Additionally, a sensation of dyspnea can also be caused by other underlying mechanism such as heart failure, fear depression, and airway irritants.[23]

Associations between respiratory function and health-related quality of life

In the present study several associations between parameters of respiratory function and HRQOL domains were found. All studied respiratory function parameters were associated with social functioning, and dyspnea (at rest and/or during activity) was associated with all studied HRQOL domains. These results were largely in agreement with conclusions in previous studies. For example, Jain et al[10] found that FVC was associated with functioning (physical and social limitations), while self-reported respiratory symptoms were associated with multiple HRQOL domains. In contrast, the association between dyspnea and mental health was not found in other studies.[7, 10] The results found in our and in previous studies suggest that respiratory function is of importance for HRQOL.

Mean scores for HRQOL in persons with severe respiratory function impairments were notably worse. This finding stresses the importance of preventing or reducing respiratory function impairments, even though severe impairments were not common. The relieve of dyspnea may improve HRQOL by 12 to 27% of the theoretical score range. Considering long term changes, excessive decline of FVC added up over many years may lead to significant negative changes in social functioning over the years (2% for each decline of 10% predicted FVC).[24]

When interpreting these results, we have to realize that the parameters of respiratory function explained only 2 to 6% of the variance in HRQOL. However, HRQOL is a difficult and complex concept that depends on many sociodemograhic, psychosocial, health, and disability related variables. There is not one variable that explains the variance of HRQOL at large.[25-27] Nevertheless, HRQOL is an important outcome in rehabilitation, and therefore, the associations found in our study may be clinically relevant.[28]

Limitations

A limitation of the present study was that FVC was not determined in all persons. This may have lowered statistical power. In addition, it is possible that especially the more vulnerable persons were not able or willing to come to the rehabilitation center for measurements, and therefore did not perform pulmonary function tests. This may have led to underestimation of impaired respiratory function. Contrary, only persons who were (partly) wheelchair dependent were included in this study, which may have led to overestimation. In addition, in order to have a realistic representation of the SCI population, the 10 persons with concomitant respiratory conditions were not excluded. This may have affected the prevalence and incidence rates. However, post hoc analysis with exclusion of these persons did not change the associations found. Furthermore, the questionnaires concerning perceived impaired respiratory function (dyspnea and cough strength) were not validated. Finally, due to the cross-sectional nature of the present study, conclusions on the direction of the relationships found cannot be made.

Clinical implications

Respiratory function impairments were present in all lesion groups. This finding indicates the need to monitor respiratory impairments in all persons with SCI irrespective of lesion characteristics. Furthermore, relationships found in this study suggest that maintaining good respiratory function is not only important to prevent respiratory infection, but also to maintain good HRQOL.

SUPPLIERS

a: CareFusion: Leibnizstrasse 7, 97204 Hoechberg, Germany.

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Chapter 5

**Resistive inspiratory muscle training
in persons with spinal cord injury
during inpatient rehabilitation:
a randomized controlled trial**

Karin Postma
Janneke A. Haisma
Maria T.E. Hopman
Michael P. Bergen
Henk J. Stam
Johannes B.J. Bussmann

ABSTRACT

Background: Persons with spinal cord injury (SCI) may benefit from resistive inspiratory muscle training (RIMT). Current evidence is weak and little is known about the effect on functional outcomes and long-term effects.

Objective: The purpose of this study was to assess immediate and long-term effects of RIMT in persons with SCI.

Design: This was a single-blinded randomized controlled trial.

Setting: The study was conducted at 4 specialized SCI units in the Netherlands.

Patients: The study participants were 40 persons with SCI (15 with motor complete tetraplegia, 16 with incomplete tetraplegia, 8 with motor complete paraplegia, and 1 with incomplete paraplegia) who had impaired pulmonary function and were admitted for initial inpatient rehabilitation.

Intervention: Study participants were randomized to an RIMT group or a control group. All participants received usual rehabilitation care. In addition, participants in the intervention group performed RIMT with a threshold trainer.

Measurements: Measurements were performed at baseline, after 8 weeks of intervention, 8 weeks later, and 1 year after discharge from inpatient rehabilitation. Primary outcome measures were: respiratory muscle function, lung volumes and flows, and perceived respiratory function. Secondary outcome measures concerned patient functioning, which included health-related quality of life, limitations in daily life due to respiratory problems, and respiratory complications.

Results: During the intervention period, maximum inspiratory pressure (MIP) improved more in the RIMT group than in the control group (11.7 cm H_2O, 95% confidence interval=4.3 to 19.0). At follow-up, this effect was no longer significant. No effect on other primary or secondary outcome measures was found except for an immediate effect on mental health.

Limitations: The sample size was insufficient to study effects on respiratory complications.

Conclusions: Resistive inspiratory muscle training has a positive short-term effect on inspiratory muscle function in persons with SCI who have impaired pulmonary function during inpatient rehabilitation.

INTRODUCTION

In most persons with acute spinal cord injury (SCI), respiratory function is seriously impaired. Even though partial recovery takes place during the first year after onset, many persons continue to have respiratory impairments (e.g. weak respiratory muscle strength, low lung volumes and flows, ineffective cough) and, consequently, elevated risk of respiratory complications.[1-6]

Traditionally, respiratory management in persons with SCI has focused on ventilation-independent breathing and on the prevention of respiratory complications such as secretion retention, atelectasis, and lower tract respiratory infection.[7, 8] It has been postulated that improvement of inspiratory muscle strength through specific training in persons with SCI may result in greater improvement of pulmonary function and cough capacity during initial recovery and may lower the risk of excessive decline in pulmonary function and respiratory complications in the chronic phase.[9-11] Resistive inspiratory muscle training (RIMT) has been shown to increase inspiratory muscle function, lung volumes, and exercise capacity in people who are healthy[12, 13] and has been shown to be effective in several patient populations.[14-18] In persons with SCI, a recent meta-analysis, reported in 2 publications,[19, 20] showed that respiratory muscle training can improve respiratory muscle strength and possibly vital capacity. However, in this meta-analysis only 3 studies concerned clinical trials studying the effects of RIMT. These studies were characterized by small sample sizes (N=12-20), and the results are conflicting.[21-23] In addition, these studies included only persons with complete tetraplegia, although it can be expected that problems with impaired respiratory function also may be present in persons with incomplete tetraplegia or thoracic lesions.[3] Furthermore, as in other types of respiratory muscle training, it is unknown whether effects of RIMT are sustained over time and result in long-term functional benefit.

The objective of the present study was to assess the immediate and long-term effects of additional RIMT in addition to the usual rehabilitation care, as compared with usual care alone, on respiratory function (respiratory muscle strength, lung volumes and flows, and perceived respiratory function) in persons with SCI who have impaired pulmonary function. In addition, we studied the effects of RIMT on measures of patient functioning (health-related quality of life (HRQOL), limitations in daily life, and of respiratory complications).

METHOD

Design overview
This study was a single-blinded multicenter randomized controlled trial, in which the effects of an added intervention (RIMT group) was compared with usual care (control group). The study was prospectively registered at the Dutch trial register (NTR1921).

Setting and participants

This trial was carried out at 4 rehabilitation centers with specialized SCI units in the Netherlands. Recruitment started in October 2009 in 3 centers, and as inclusion rate was slow, a fourth center was added in June 2011. Inclusion criteria were: persons with SCI admitted for initial inpatient rehabilitation; motor level T12 or higher; American Spinal Injury Association Impairment Scale (AIS) A, B, C or D[24]; age 18 to 70 years; and impaired pulmonary function. Impaired pulmonary function was defined as forced expiratory volume in 1 second (FEV_1) below 80% of the predicted value. Exclusion criteria were: progressive diseases, a psychiatric condition that interfered with constructive participation, insufficient comprehension of the Dutch language, medical instability, ventilator dependency, and the presence of tracheostomy. The Medical Ethics Committee of the Erasmus University Medical Center in Rotterdam, the Netherlands, approved the study. All patients gave informed consent.

Randomization and interventions

For each center a randomization schedule for 2 separate arms (arm A for persons with FEV_1 below 60.0% of the predicted value and arm B for persons with FEV_1 between 60.0% and 79.9% of the predicted value) was computer generated. The randomization schedules were constructed with blocks of two, to ensure equal distribution over the RIMT group and the control group. The allocation sequence was concealed by using consecutively numbered, sealed envelopes. After the baseline measurement, a physical therapist working at the SCI unit opened the first numbered envelope of the corresponding arm containing the group allocation. None of the individuals involved in the allocation, were aware of which method was used to construct the randomization schedules. This blinding, together with the separate randomization schedules for 2 separate arms, ensured that the allocation sequence was concealed until opening the envelope.

The study was set up as a pragmatic trial. The intervention started 5 weeks after the start of active inpatient rehabilitation (defined as out of bed for at least 3 consecutive hours). All participants received usual care (including passive range of motion, muscle strength exercises, and functional training) and 2 standardized educational lessons on general aspects of respiratory function and respiratory complications. Persons allocated to the RIMT group trained 8 weeks with an IMT Threshold trainer (Threshold IMT, Respironics Inc, Parsippany, New Jersey, USA), 5 times a week, according to an interval-based, high-intensity protocol. This protocol was found to be feasible[25] and effective[26] in persons with chronic obstructive pulmonary disease (COPD). The intended load at the start of the training was 60% of maximal inspiratory pressure (MIP) at baseline. Each training session consisted of 7 sets of 2 minutes breathing through the Threshold trainer followed by 1 minute of un-resisted breathing. To get acquainted with the training, sets were increased from 3 to 7 in the first week. At each center, one physical therapist employed at the SCI unit and instructed verbally and in writing was responsible for the execution of the protocol. This therapist evaluated the training and increased the threshold load once a week. Other training sessions were planned as part of the overall rehabilitation program and supervised (throughout each training session) by an assistant. For all training sessions during the intervention period, duration and intensity were recorded in a logbook. In addition, the intervention was subjectively evaluated with a

written questionnaire at the end of the intervention period. After completion of the intervention period, participants in the RIMT group were advised by the therapist to continue RIMT. Whether participants continued training was determined retrospectively by written questionnaires at set time-points: 8 weeks after the intervention period, and 3, 6, 9, and 12 months after discharge from inpatient rehabilitation.

Outcome measures and follow-up

Measurements were performed in the week before the start of the intervention period (baseline: T0), within 1 week after the intervention period (T1), 8 weeks after T1 (T2), and 1 year after discharge of inpatient rehabilitation (T3). All measurements, with the exception of respiratory complications, were performed by a research assistant who was not involved in treatment of the participant and not aware of the group allocation. Lesion characteristics, secondary complications and comorbidity were recorded by the attending physician at all measurement occasions. Motor loss and sensory loss were scored according to the Dutch translation of the International Standards for Neurological Classification of Spinal Injury developed by the American Spinal Injury Association (ASIA).[24]

Primary outcome measures of this study were objective and subjective measurements of respiratory function. Respiratory muscle strength was determined by MIP (also known as PImax) and maximum expiratory pressure (MEP, also known as PEmax), both measured at the mouth with the MicroRPM (CareFusion, Basingstoke, United Kingdom) using a flanged mouth piece and expressed in cm H_2O.[27, 28] Maximum inspiratory pressure was measured after full expiration, and MEP was measured after full inspiration. Maximum pressure had to be maintained for at least 1 second. The highest value of 8 maneuvers that varied less than 5% from the next value was recorded and used for analysis. Lung volumes and flows were measured with a spirometer (Oxycon Delta, CareFusion, Hoechberg, Germany). Forced vital capacity (FVC), FEV_1, and peak expiratory flow (PEF) were measured according to the American Thoracic Society standards modified for people with SCI.[29, 30] Three to 5 repeated flow volume curves were performed. Outcomes of the best trial (the trial with the highest sum of FVC and FEV_1) was used for analysis. Maximum ventilation volume (MVV), a measure of respiratory muscle endurance, was measured during 12 seconds of maximal deep inspiration and expiration at a set pace of 60 breaths per minute.[27] The pace was controlled using a metronome and the highest value of 3 maneuvers was used for analysis. To establish cough capacity, participants were asked to cough as forcefully as possible after full inspiration.[31] The highest value of 8 maneuvers that varied less than 5% from the next value was recorded as peak cough flow (PCF) and used for analysis.

All measures of objective respiratory function were determined with persons seated in their own wheelchair, using a nose clip, and with abdominal binders (if present) removed. Perceived respiratory functioning was assessed with a questionnaire. Persons were asked to what extent they experienced limitations with breathing (when sitting quietly, positioned supine, or during exercise), talking (when speaking loudly, in long sentences, or more than a few minutes), and coughing and clearing one's nose on a numeric visual analog scale (0=no effort, 10=not possible). A mean score (0 to 10) for the breathing, talking and cough/sneeze function was calculated; higher scores reflect worse functioning.

Secondary outcome measures concerned different aspect of patient functioning: HRQOL, perceived limitations in daily life, and respiratory complications. Three subdomains of HRQOL - perceived general health, mental health (psychological functioning), and vitality (energy and fatigue) - were measured with the corresponding subscales of the 36-Item Short Form Health Survey questionnaire (SF-36).[32] In each subscale, scores were added and transformed to a score of 0 (lowest) to 100 (highest). High scores reflect better HRQOL. The SF-36 has been proven to be reliable and valid in people with SCI.[33, 34] Furthermore, persons reported to what extent they felt limited in daily life due to respiratory problems on a 7 point scale (1=not at all, 7=completely limited). The incidence of respiratory complications within the first year after discharge of inpatient rehabilitation was assessed in two ways. One year after discharge (at T3), the physician registered whether the person had received treatment for respiratory complications during the previous year (physician-reported respiratory complications). In addition, persons were asked by written questionnaire, every three months after discharge, whether they had had any increased breathlessness, increased phlegm, fever due to respiratory infection, or other respiratory problems (patient-reported respiratory complications).

Data analysis

The sample size was determined with power analysis based on FVC. Given this outcome measure, an expected additional treatment effect of 10%, a standard deviation of 12%, a power of 80%, a significance level of .05, and a 10% dropout rate, we calculated that 20 patients in each group were needed.

To test the potential effect when performing RIMT, a per-protocol analysis was used. Per-protocol analysis was chosen above intention-to-treat analysis to allow clinicians to offer this intervention based on the estimated actual effect (effect of persons who follow the training) as opposed to the estimated effect in a group of persons who were offered the treatment. Only persons who adhered to the protocol and performed at least one follow-up measurement, were included in the analysis. Center-specific effects were not of interest for this trial; therefore the data of participants from each center were pooled together. Generalized estimating equation analysis was used to determine the between-group differences. The measurement occasion (as the factor time), group (RIMT or control) and time x group interaction were added to the model as independent variables. The group variable represents the between-group differences and thus the intervention effect. Baseline values were added to the model as covariates to control the intervention effect for baseline differences. By changing the sequence of the factor time, effects at different follow-up periods were calculated: short-term (T0 – T1), medium-term (T0 – T2), and long-term (T0 – T3). Limitations in daily life and respiratory complications were described in numbers and percentages. All statistical analyses were performed with IBM SPSS version 20 (IBM Corp, Armonk, New York), and level of significance was set at P<.05.

Role of the funding source

Enrollment

Assessed for eligibility (N=86)

Excluded (n=42)
- Did not meet inclusion criteria (n=21)
- Declined to participate (n=18)
- Other reasons (n=3)

T0: Baseline

Randomized (n=44)

Allocation

Allocated to the RIMT group (n=22),
center A (n=11), B (n=6), C (n=5), D (n=0)
- Received allocated intervention (n=21)
- Excluded due to psychiatric condition (n=1)

Allocated to control group (n=22),
center A (n=10), B (n=7), C (n=4), D (n=1)
- Received allocated intervention (n=21)
- Excluded due to psychiatric condition (n=1)

Follow-Up

T1: After intervention period (n=19)
Lost to follow-up (n=1: medical problems)
Discontinued intervention (n=1)

T1: After intervention period (n=21)
Lost to follow-up (n=0)

T2: + 8 weeks (n=18)*
Lost to follow-up (n=1: declined further participation)

T2: + 8 weeks (n=20)
Lost to follow-up (n=1: not able to contact)

T3: 1 year after inpatient rehabilitation (n=14)
Lost to follow-up (n=4: declined further participation [n=2], medical complication [n=2])

T3: 1 year after inpatient rehabilitation (n=15)
Lost to follow-up (n= 5: declined further participation [n=3], not able to contact [n=1], medical complication [n=1])

Analysis

Analyzed per protocol (n=19)
- Excluded from analysis (n=3)

Analyzed per protocol (n=21)
- Excluded from analysis (n=1)

Figure 1. CONSORT flow diagram of study participation from enrolment to analysis. RIMT=resistive inspiratory muscle training. *Indicates data missing for 2 participants.

RESULTS

Study population

The first person enrolled in the trial on October 1, 2009 and the last person enrolled on July 7th 2012. Figure 1 is a flow diagram of study participation from enrollment to analysis. After randomization, 2 persons were excluded because of psychiatric conditions, 1 person discontinued the training due to decline in overall function, and 1 person was not available for the follow-up measurements.

The study group (N=40) consisted of 35 men (87.5%) and 5 women (12.5%), and the mean age at baseline was 46.8 years (SD=14.3). Fifteen participants had motor complete tetraplegia, 15 had incomplete tetraplegia, 9 had motor complete paraplegia (lowest level T9), and 1 had incomplete paraplegia (T7). Table 1 presents the personal and lesion characteristics for the RIMT group and control group at baseline. By chance, all participants with concomitant respiratory diseases (2 had asthma, and 4 had COPD) were allocated to the control group.

Table 1. Characteristics at baseline for the RIMT group and Control group

Characteristics	RIMT group (n=19)	Control group (n=21)
Personal characteristics		
Age in years, mean ± SD	47.1 ± 14.1	46.6 ± 14.9
Men, n (%)	18 (94.7)	17 (81.0)
Smoking status*, smoker, n (%)	9 (47.4)	11 (52.4)
Lesion characteristics		
Tetraplegia, n (%)	12 (63.2)	18 (85.7)
Motor complete lesion, n (%)	13 (68.4)	11 (52.4)
Days since injury, median (IQR)	74 (57-109)	88 (59-121)
Days since admission, median (IQR)	47 (29-76)	35 (32-58.5)
Traumatic cause, n (%)	16 (84.2)	18 (85.7)
Respiratory comorbidity		
Mechanical ventilation, n (%)	9 (47.4)	10 (47.6)
Thorax or lung trauma, n (%)	7 (36.8)	5 (23.8)
Premorbid respiratory diseases, n (%)	0 (0)	6 (28.6)

IQR=interquartile range. *Smoking status at onset of spinal cord injury.

Training

On average, 39 training sessions (SD=4, range:30 to 47) were performed by the RIMT group during the intervention period. The mean training load increased from 50% (SD=15%) to 77% (SD=33%) of baseline MIP. Six persons achieved the maximum possible resistance of the Threshold trainer (41 cm H_2O) before the end of the intervention period and continued to increase the training dose by lengthening the time breathing against resistance and shortening the time without resistance. Eight persons continued training at a regular base (2 to 3 times a week) at least until 8 weeks after the intervention period, and some continued several months after discharge from inpatient rehabilitation. Nobody continued training during the full follow-up time.

Table 2. Descriptive results for the RIMT group and Control group

	RIMT group				Control group			
	Baseline (n=19)	After intervention period (n=19)	+ 8 weeks (n=16)	1 year after inpatient rehabilitation (n=14)	Baseline (n=21)	After intervention period (n=21)	+ 8 weeks (n=20)	1 year after inpatient rehabilitation (n=15)
Respiratory muscle strength								
MIP (cm H$_2$O)	56.4 ± 29.5	82.7 ± 29.7	82.2 ± 24.5	102.4 ± 33.9	56.1 ± 23.5	70.7 ± 28.1	74.1 ± 28.5	85.6 ± 30.4
MEP (cm H$_2$O)	39.7 ± 20.3	53.5 ± 25.7	52.3 ± 24.3	70.4 ± 35.0	52.9 ± 30.0	61.7 ± 27.9	64.6 ± 31.1	64.6 ± 30.3
Lung volumes and flows								
FVC (l)	2.67 ± 0.83	3.09 ± 0.96	3.11 ± 0.81	3.53 ± 1.26	3.10 ± 1.10	3.51 ± 1.11	3.58 ± 1.10	3.85 ± 1.28
FEV1 (l)	2.11 ± 0.68	2.43 ± 0.80	2.49 ± 0.53	2.75 ± 0.97	2.18 ± 0.75	2.48 ± 0.81	2.56 ± 0.86	2.91 ± 1.06
PEF (l/s)	4.22 ± 1.71	4.94 ± 2.20	5.04 ± 1.77	5.96 ± 2.59	4.10 ± 1.69	4.59 ± 1.61	4.84 ± 1.70	5.43 ± 1.60
MVV (l/min)	65.7 ± 29.3	77.5 ± 29.4	74.1 ± 28.4	88.6 ± 39.3	55.2 ± 26.8	69.3 ± 32.2	74.0 ± 31.8	78.8 ± 32.6
PCF (l/s)	5.32 ± 1.69	6.08 ± 1.80	5.99 ± 1.81	7.24 ± 1.99	4.83 ± 1.97	5.53 ± 2.13	5.62 ± 1.92	5.96 ± 1.69
Perceived respiratory function								
Breathing function (0-10)	1.67 (1.00-3.00)	1.00 (0.33-1.67)	0.50 (0.00-2.25)	0.67 (0.00-2.08)	1.33 (0.33-3.33)	0.67 (0.00-1.17)	0.50 (0.00-1.33)	0.00 (0.00-0.67)
Talking function (0-10)	4.33 (1.33-6.00)	1.33 (0.67-4.67)	3.00 (0.75-4.25)	1.50 (0.58-3.75)	3.67 (0.83-5.67)	2.00 (0.00-3.83)	1.17 (0.00-3.33)	0.00 (0.00-3.67)
Cough/sneeze function (0-10)	6.50 (2.50-7.50)	4.50 (2.00-5.50)	3.25 (1.13-5.00)	2.25 (1.38-4.25)	4.00 (1.00-6.00)	2.00 (0.00-4.25)	1.50 (0.50-3.75)	3.00 (0.50-3.00)
Health-related quality of life								
General health (0-100)	56.6 ± 19.9	58.7 ± 21.3	60.9 ± 18.8	65.7 ± 22.9	61.4 ± 25.1	67.3 ± 22.4	58.7 ± 22.9	64.7 ± 22.0
Mental health (0-100)	70.7 ± 18.4	76.2 ± 15.2	72.5 ± 15.2	78.6 ± 12.6	73.5 ± 15.4	66.6 ± 20.2	74.1 ± 15.2	74.7 ± 16.0
Vitality (0-100)	59.5 ± 16.2	61.8 ± 15.9	64.4 ± 13.3	70.4 ± 18.4	66.9 ± 17.7	63.6 ± 16.4	70.0 ± 16.2	67.0 ± 17.4

Outcomes of respiratory muscle strength, lung volumes and flows, and health-related quality of life are presented as mean ± SD; higher scores indicate better functioning. Results of perceived respiratory function are presented as median (interquartile range); higher scores indicate worse functioning. RIMT=resistive inspiratory muscle training, MIP=maximal inspiratory pressure, MEP=maximal expiratory muscle pressure, FVC=forced vital capacity, FEV1=forced expiratory volume in 1 second, PEF=peak expiratory flow, MVV=maximum ventilation volume, PCF=peak cough flow.

Effects of RIMT

Table 2 presents the respiratory function and HRQOL at all measurement occasions. Generalized estimating equation analysis showed significant improvement over time in all parameters except for the subdomains of HRQOL for the entire study group. During the intervention period, the RIMT group showed greater improvement in MIP compared with the control group (Table 3). This between-group difference partially sustained but was no longer statistical significant at follow-up. The change in MIP over time for the RIMT group and the control group is graphically presented in Figure 2. Additional exploratory analyses indicated that MIP improved over a longer period in persons who continued RIMT after the intervention period compared with those who discontinued RIMT (Figure 3). In none of the other measures of respiratory function were between-group differences found.

Table 3. Mean differences in change between the RIMT group and Control group at Short-term, Medium-term, and Long-term follow-up

	Short-term follow-up (T0 – T1)			Medium-term follow-up (T0 – T2)			Long-term follow-up (T0 – T3)		
Measure	Mean difference	95% CI	P	Mean difference	95% CI	P	Mean difference	95% CI	P
Respiratory muscle strength									
MIP (cm H$_2$O)	11.67	4.33-19.02	.002	9.75	−0.61-20.11	.065	8.33	−6.51-23.17	.271
MEP (cm H$_2$O)	2.65	−8.55-13.85	.642	0.09	−13.50-13.68	.989	5.07	−10.70-20.83	.529
Lung volumes and flows									
FVC (l)	−0.04	−0.30-0.22	.779	−0.02	−0.34- 0.30	.918	−0.10	−0.68-0.48	.733
FEV1 (l)	0.02	−0.22-0.26	.845	0.04	−0.22-0.31	.746	−0.13	−0.58-0.31	.556
PEF (l/s)	0.25	−0.53-1.03	.526	0.14	−0.70-0.99	.737	0.03	−0.96-1.02	.952
MVV (l/min)	−1.16	−12.26-9.94	.838	−3.13	−16.45-10.19	.645	0.58	−13.38-14.54	.935
PCF (l/s)	0.16	−0.52-0.83	.647	0.17	−0.55-0.89	.640	0.80	−0.02-1.61	.055
Perceived respiratory function									
Breathing function (0-10)	0.09	−0.61-0.78	.808	0.31	−0.41-1.03	.401	0.52	−0.15-1.18	.127
Talking function (0-10)	−0.28	−1.50-0.94	.652	0.74	−0.32-1.79	.170	0.44	−0.86-1.75	.506
Cough/sneeze function (0-10)	0.49	−0.74-1.72	.433	0.60	−0.53-1.73	.299	0.31	−1.11-1.73	.667
Health-related quality of life									
General health (0-100)	−5.47	−15.12-4.19	.267	4.95	−4.64-14.54	.312	8.06	−2.86-18.99	.148
Mental health (0-100)	11.45	3.24-19.65	.006	1.08	−5.68-7.85	.754	7.63	−0.20-15.46	.056
Vitality (0-100)	1.54	−7.76-10.84	.745	−1.67	−9.22-5.89	.666	7.59	−2.58-17.75	.144

The mean difference represents the intervention effect for the corresponding time period corrected for baseline value. For respiratory muscle strength, lung volumes and flows, and health-related quality of life, a significant positive mean difference presents a positive intervention effect. For perceived respiratory function, a negative mean difference presents a positive intervention effect. RIMT=resistive inspiratory muscle training, T0=baseline (measurements performed in the week before the start of the intervention period), T1=1 week after the intervention period, T2=8 weeks after T1, T3=1 year after discharge from inpatient rehabilitation, 95% CI=95% confidence interval, MIP=maximal inspiratory pressure, MEP=maximal expiratory muscle pressure, FVC=forced vital capacity, FEV1=forced expiratory volume in 1 second, PEF=peak expiratory flow, MVV=maximum ventilation volume, PCF=peak cough flow.

With the exception of mental health, no between-group differences were found for secondary outcome measures. The RIMT group showed greater improvement in mental health compared with the control group after the intervention period. In both groups, the number of persons who perceived limitations in daily life ("very little" to "fully") decreased similarly over time (in the RIMT group, the incidence was 68% at T0, 32% at T1, 44% at T2, and 36% at T3; in the control group, the incidence was 62% at T0, 33% at T1, 50% at T2, and 33% at T3). Physicians reported respiratory complications in 3 persons of the RIMT group (upper tract respiratory infection, pneumonia, and nocturnal dyspnea) and 2 persons of the control group (upper tract respiratory infection and nocturnal dyspnea) during the year after inpatient rehabilitation. In addition, 6 persons in the RIMT group and 7 persons in control group reported increased breathlessness, increased phlegm, fever due to respiratory infection, or other respiratory problems.
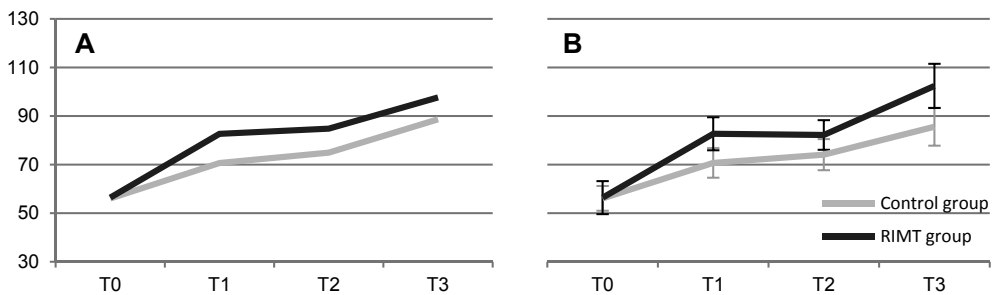
Figure 2. Change of maximum inspiratory pressure (in cm H2O) over time in the resistive inspiratory muscle training (RIMT) group and control group, based on (A) generalized estimating equation analysis and (B) raw data (mean and standard error of the mean). T0=baseline (measurements performed in the week before the start of the intervention period), T1=1 week after the intervention period, T2=8 weeks after T1, T3=1 year after discharge from inpatient rehabilitation.

DISCUSSION

In the present randomized clinical trial, we studied the effect of an added RIMT program, as compared with the usual inpatient rehabilitation care alone, in persons with SCI who have impaired pulmonary function. In addition to the effect on respiratory function, we also studied the effect on several aspects of patient functioning. To our knowledge, this is the first study concerning RIMT in which long-term effects and the effect on respiratory complications were studied. Resistive inspiratory muscle training had an immediate positive effect on MIP, but this effect was no longer significant after long-term follow-up. No effects on other parameters of respiratory function were found. With exception for an immediate effect on mental health, we found no effect on other measures of patient functioning (HRQOL, limitations in daily life due to respiratory problems, or the incidence of respiratory complications).

We found positive effects of RIMT on MIP. These effects were found after per-protocol analysis; therefore the results are only for persons who actually performed RIMT. These results strengthen the conclusion

of a recently published randomized clinical trial on RIMT[23] and a meta-analysis on respiratory muscle training in general.[19, 20] The short-term additional effect of RIMT on MIP found in our study (11.7 cm H_2O) was comparable to the pooled effect of the previously mentioned meta-analysis (10.7 cm H_2O)[20] but lower than the effect found by Mueller et al (26.5 cm H_2O).[23] However, in that study a different control intervention was applied. When considering the relative improvements in the RIMT groups, the results were quite similar (46.6% in our study versus 53.6% in the study of Mueller et al[23]), despite lower training intensities in our study (50% to 70% of baseline MIP versus 80% of actual MIP). Improvement of MIP during the first months after onset of SCI may be of great importance in this population. After all, in acute SCI, respiratory muscle function is often severely impaired, and medical complications lurk.[2] Well-preserved inspiratory muscle function is essential in maintaining adequate gas exchange during quiet breathing and in situations of increased respiratory demand (during exercise, strenuous work such as wheelchair propelling or making transfers, and during periods of illness or respiratory complications).[35, 36] The positive short-term effect on MIP found in our study was partially sustained at follow-up but was no longer statistically significant. A large part of the sustained effect 8 weeks after the intervention appeared to be due to the 8 persons who continued RIMT after the intervention period. This finding suggests that a longer training period may prolong the effect of RIMT on MIP. Perhaps for long-term effects, maintenance training may be needed, as previously reported in persons with COPD.[37]

Based on previously found associations between inspiratory muscle function on the one hand and lung volumes[38] and cough flows[9] on the other, it could be expected that RIMT would indirectly (through improved MIP) improve lung volumes and flows. Nevertheless, the present study showed no effect on lung volumes and flows. The lack of an immediate effect on FVC is in agreement with results of Mueller et al[23] but does not coincide with the positive effect on vital capacity found in the study on RIMT by Liaw et al[22] and the meta-analysis on respiratory muscle training in general.[19, 20] As pointed out by the authors
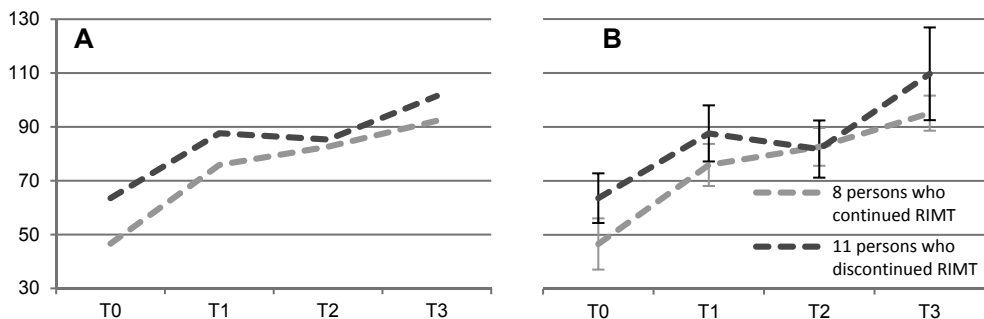
Figure 3. Change of maximum inspiratory pressure (in cm H2O) over time in 2 subgroups within the resistive inspiratory muscle training (RIMT) group, based on (A) generalized estimating equation analysis and (B) raw data (mean and standard error of the mean). T0=baseline (measurements performed in the week before the start of the intervention period), T1=1 week after the intervention period, T2=8 weeks after T1, T3=1 year after discharge from inpatient rehabilitation.

of that meta-analysis, the effect they found was not strong (small effect size and small number of studies) and may have been overestimated due to uncontrolled differences at baseline. The aforementioned associations among inspiratory muscle function, lung volumes, and cough flows may be complex and cumulative of nature. Factors such as concomitant trauma of lung tissue and thorax, spasticity of the trunk muscles, and the degree of preservation of expiratory muscle may play an important role. In addition, over time, the inability to inspire deeply (due to weak inspiratory muscle strength) may lead to a cascade of reduced compliance of lung and thorax, lowered reserve capacity of the respiratory pump, increased susceptibility for medical complications,[35] recurrent respiratory infections and gradual deterioration of lung tissue. The latter may explain the associations between low MIP and excessive decline in FVC in persons with chronic SCI found in previous studies.[10, 11]

With the exception of a short-term effect of RIMT on mental health, no effects were found on measures of patient functioning. The specific short-term effect of RIMT on mental health may be explained by the extra attention participants in the RIMT group received and their trust in a positive effect. However, this explanation has not a strong basis; therefore, especially in combination with the possible effect of multiple testing for which we did not correct in our analyses, we have to be careful in drawing firm conclusions. Another important aim of this trial was to study the effects on respiratory complications. The results did not indicate a positive effect of RIMT on respiratory complications. However, the power analysis was based on respiratory function measures and not on respiratory complications; therefore, interpretation of these results should be done with caution. To attain better insight into the effect of respiratory muscle training on long-term respiratory complications, large-scale studies with a long (several years) follow-up time are necessary. In addition, research is needed to study whether respiratory complications during the acute phase can be prevented when RIMT is started shortly after injury. In the present study, for methodological reasons, the intervention started relatively late. Nevertheless, RIMT also can be performed by patients still immobilized in bed, with a tracheostomy or even in combination with mechanical ventilation.

In this trial, RIMT was successfully conducted in 3 different SCI units without large changes in care or organization. The positive effect of RIMT on MIP did not differ among these units. In general, administration of the training delivered no problems. A short instruction, face-to-face and on paper, was sufficient to instruct the therapists. Additionally, the training sessions fitted within the regular structure of half-hour treatment schedules, and the majority of training sessions were performed with little supervision. Persons with restricted hand function needed personal assistance to start and finish the training and a simple homemade stand to position the device. Furthermore, most persons were able to handle the trainings device independently, and some used the device at home. The majority of persons in the RIMT group were satisfied (13 of 19 persons) or somewhat satisfied (4 persons) about the training. In contrast to previous studies, we included not only persons with complete tetraplegia but also those with incomplete tetraplegia or paraplegia who had impaired pulmonary function. Therefore, the results of this study may be generalized to all persons with SCI who have impaired pulmonary function, regardless of lesion level. However, the results of the present study (e.g. a positive immediate effect on MIP) suggest that

RIMT may be especially beneficial in persons with weakness of the inspiratory muscles. Therefore, MIP may be a better indicator for RIMT than impaired pulmonary function.

A limitation of the present study may have been the uneven distribution of persons with premorbid respiratory diseases between groups (all were allocated to the control group). However, post-hoc analysis showed that conclusions concerning the effect of RIMT on MIP did not change when the data of these individuals were excluded. Nevertheless, because of the uneven distribution, the present study does not answer the question whether the proven positive effects of RIMT in persons with COPD or asthma also apply after SCI.[15, 39] Another limitation was that the questionnaires on perceived respiratory function, limitations in daily life, and respiratory complications were not validated and may not have been sensitive enough to detect differences between groups. In addition, the relatively large number of dropouts 1 year after inpatient rehabilitation caused a loss of power, which may have influenced the results concerning long-term follow-up. Finally, due to the low incidence rates, the sample size may have been too small to show long-term effects on respiratory complications. Altogether, interpretation of the long-term effects on patient functioning has to be done with caution.

In conclusion, RIMT has a positive short-term effect on inspiratory muscle function and is a feasible and important addition to the usual inpatient rehabilitation of persons with SCI who have impaired pulmonary function, regardless of lesion level. To sustain the effect over a longer time period, the training periods may have to be extended. Based on the results of this study, it is not possible to make conclusions regarding the long-term effects of RIMT on respiratory complications. Future research is needed to attain better insight into the underlying mechanisms of respiratory muscle training and the effect on respiratory complications.

ACKNOWLEDGEMENTS

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Chapter 6

Longitudinal relationship between respiratory muscle strength and cough capacity in persons with spinal cord injury

Karin Postma
Lonneke Y.M. Vlemmix
Janneke A. Haisma
Sonja de Groot
Tebbe A.R. Sluis
Henk J. Stam
Johannes B.J. Bussmann

ABSTRACT

Objective: to assess the longitudinal relationship between respiratory muscle strength and cough capacity in persons with recent spinal cord injury (SCI).

Design: longitudinal analyses

Subjects: 40 persons with recent SCI who had impaired pulmonary function

Methods: Measurements were performed 4 weeks after the start of rehabilitation, 9 and 17 weeks after the first measurement, and one year after discharge from inpatient rehabilitation. Peak cough flow (PCF) was measured with a spirometer. Maximum inspiratory and maximum expiratory pressure were measured at the mouth (MIP and MEP, expressed in cm H_2O).

Results: Both MIP and MEP were significantly positively associated with PCF. A 10 cm H_2O higher MIP was associated with a 0.32 l/sec higher PCF, and a 10 cm H_2O higher MEP was associated with a 0.15 l/sec higher PCF. The association between MIP and PCF was mainly based on within-subject variance; a change in MIP with 10 cm H_2O was associated with a change in PCF with 0.27 l/sec. The association between MIP and PCF was stronger than between MEP and PCF.

Conclusion: Improvement of respiratory muscle strength may lead to improvement in cough capacity in persons with recent SCI who have impaired pulmonary function.

INTRODUCTION

Respiratory complications are a common cause of morbidity, hospitalization and death in the acute as well as in the chronic phase after spinal cord injury (SCI).[1-4] In this population a weak cough plays an important role in the development of serious respiratory complications such as atelectasis and pneumonia.[5, 6] Cough is an important defense mechanism that serves to clear the airways from foreign material (in aspiration) and secretions (during infections).[7] In order to decrease the risk of respiratory complications, improvement of cough is an important goal in SCI-rehabilitation.[8] Even though coughing is mainly characterized by forced expiratory activity, sufficient pre-cough inspiration is needed for it to be effective.[7] Therefore, both inspiratory muscles (to obtain a sufficient pre-cough volume) and expiratory muscles (to generate a high thoraco-abdominal pressure) are important to produce an effective cough. Previous studies in persons with SCI showed that both inspiratory and expiratory muscle strength were associated with cough.[9 10] Based on these results it was suggested that training of respiratory muscle strength may improve cough capacity. However, these studies were based on cross-sectional data, and therefore, it is possible that these associations mainly reflect differences between persons and not within persons. In addition, associations were only studied in persons with complete tetraplegia and not corrected for factors such as age, body mass, smoking history, respiratory diseases, concomitant trauma, activity level, and spasticity. Altogether, it remains unclear whether improvement of respiratory muscle strength (spontaneous or by training) leads to improved cough. Better understanding of the relationship between respiratory muscle strength and cough may help design intervention programs that aim at improving cough effectiveness and help decrease the risk of respiratory complications. Therefore, the objective of the present study was to assess the longitudinal relationship between respiratory muscle strength and cough capacity in persons with recent SCI.

METHODS

Participants

For the present study we used data from a recently conducted RCT in which the effects of an added intervention (resisted inspiratory muscle training: RIMT) was compared to usual care.[11] This trial was carried out at 4 rehabilitation centers with specialized SCI units in the Netherlands. Inclusion criteria were: persons with SCI admitted for initial inpatient rehabilitation, motor level Thoracic 12 or higher, American Spinal Injury Association Impairment Scale (AIS) A, B, C or D, age 18 to 70 year, and impaired pulmonary function. Impaired pulmonary function was defined as forced expiratory volume in one second (FEV_1) below 80% of the predicted value. Exclusion criteria were: progressive diseases, psychiatric condition that interfered with constructive participation, insufficient comprehension of the Dutch language, medical instability, ventilator dependency and the presence of tracheostomy. The Medical Ethics Committee of the Erasmus University Medical Centre in Rotterdam, the Netherlands, approved the study and all participants gave informed consent.

Procedures

Measurements were performed four times. The first measurement (T0) was performed four weeks after the start of active inpatient rehabilitation (defined as: out of bed for at least 3 consecutive hours) or shortly after closure of the tracheotomy. The follow-up measurements were performed approximately 9 weeks after T0 (T1), 17 weeks after T0 (T2), and one year after discharge of inpatient rehabilitation (T3). After the first measurement, persons were randomly allocated to the intervention group or control group. Persons in the intervention group performed RIMT between T0 and T1. More detailed information on the intervention and allocation method has been described previously.[11]

Measurements

Cough capacity

Cough capacity was measured with a spirometer (Oxycon Delta[a]: CareFusion, Hoechberg, Germany). Persons were asked to cough as forcefully as possible after full inspiration through the mouth piece.[12] This maneuver was repeated eight times. The highest value that varied less than 5% with the next value was recorded as peak cough flow (PCF) and used for analysis.

Respiratory muscle strength

Respiratory muscle strength was determined by maximum inspiratory and maximum expiratory pressure measured at the mouth (MIP and MEP, expressed in cm H_2O) with the MicroRPM[b] (CareFusion, Basingstoke, U.K.) using a flanged mouth piece;[13] MIP was measured after full expiration and MEP after full inspiration. Maximum pressure had to be maintained for at least 1 second. The highest value of eight maneuvers, that varied less than 5% with the next value was recorded and used for analysis. All measurements were performed with persons seated, using a nose clip, and with abdominal binders (if present) removed.

Personal and lesion characteristic

Personal characteristics included age at the first test occasion, gender, smoking history (pack years before onset SCI=number of cigarettes smoked per day × number of years smoked/20), body mass index (BMI=body mass divided by square height), prevalence of premorbid lung diseases such as asthma or COPD, and mobility (passive: with assistance or motorized wheelchair, or active: by manual wheelchair or walking). Lesion characteristics included lesion level (tetraplegia or paraplegia) and lesion completeness (motor complete AIS AB or incomplete AIS CD),[14] cause of SCI (traumatic or non-traumatic), prevalence of trauma of the chest or lungs at onset of SCI (such as rib fractures, pneumothorax, and lung contusion), and spasticity. Spasticity was assessed by a questionnaire in which persons were asked to rate hindrance of spasticity during: sleep, transfers, washing and dressing, wheelchair propulsion, and other activities, ranging from 0 to 2 (0=no hindrance due to spasticity; 1=little hindrance due to spasticity; 2=a lot of

hindrance due to spasticity). A sum score was computed ranging from 0 (no hindrance during any activity) to 10 (a lot of hindrance during all activities).

Statistical analyses

To study the longitudinal relationship between respiratory muscle strength and cough, generalized estimating equation analyses (GEE) with an exchangeable correlation structure were used.[15] Separate models for MIP and MEP were built. Each model contained PCF as dependent variable, the determinant time as a set of 3 dummy variables, and the independent variable MIP or MEP.

The potential confounding effect of group allocation, personal characteristics, lesion characteristics, respiratory history, and activity level on the relationship between respiratory muscle strength and cough, was studied. A variable was considered a confounder if the regression coefficient (beta) of the independent variable (MIP or MEP) changed more than 10% after adding the potential confounder to the model. Some variables were entered as time-independent variables: group allocation (RIMT-group or control-group), age (at T0), gender, smoking history (pack years before onset of SCI), level (tetraplegia or paraplegia) and completeness (AIS A and B or AIS C and D) of lesion, cause of SCI (traumatic or non-traumatic), lung or chest trauma at onset of SCI (present or not), and respiratory history (premorbid diseases present or not). Others were entered as time-dependent variables (outcomes at each test occasion): BMI, spasticity, and mobility (passive or active). A multivariate model was made with time, the independent variable (MIP or MEP) and all confounders. Finally, to detect whether the regression coefficient of the models described above, reflected mainly between-subject variance (cross-sectional relationship) or within-subject variance (longitudinal relationship), models based on change variables were made. In the change models, a change in PCF for every time interval between successive test occasions was used as the dependent variable. Change scores for MIP and MEP were used as independent variables. If the results of the standard models and the change models showed similar relationships, the associations between independent variables and cough are mainly based on within-subject variance. If not, the associations are mainly based on between-subject variance. Potential confounders were studied similarly as in the standard model. All data were analyzed using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 20.0. The statistical significance was set at $P<.05$.

RESULTS

Forty persons were included; 4 persons dropped out at T2 and 11 persons at T3. Characteristics are presented in Table 1. Table 2 presents the descriptive data of PCF, MIP, MEP, and the time-dependent confounders.

The basic GEE models showed a significant association between MIP and PCF (beta=0.028, P=.006) and between MEP and PCF (beta=0.017, P=.001). After correction for confounders these associations remained significant (Table 3). Smoking history was a confounder for the association between MIP and

PCF, and BMI was a confounder for the association between MEP and PCF. After correction for confounders, a 10 cm H_2O higher MIP was associated with a 0.32 l/sec higher PCF, and a 10 cm H_2O higher MEP was associated with a 0.15 l/sec higher PCF.

After correction for confounders, the change model (Table 4) showed a significant association between change in MIP and change in PCF; an improvement of 10 cm H_2O in MIP was associated with an improvement of 0.27 l/sec in PCF. There was a trend for an association between change in MEP and change in PCF. When both (change in) MIP and (change in) MEP were entered to a multivariate model, (change in) MEP was no longer associated with PCF.

Table 1. Personal and lesion characteristics

Age in years, mean ± SD	46.8 ± 14.3
Men, n (%)	35 (87.5)
Smoking history in pack years, median (IQR)	11.3 (0.0-20.0)
Lesion, n (%)	
Motor complete tetraplegia	15 (37.5)
Incomplete tetraplegia	15 (37.5)
Motor complete paraplegia	9 (22.5)
Incomplete paraplegia	1 (2.5)
Cause of SCI, traumatic, n (%)	34 (85.0)
Lung or chest trauma at onset SCI, n (%)	15 (37.5)
Premorbid lung disease, n (%)	6 (15.0)
Allocated to RIMT group, n (%)	19 (47.5)

Abbreviations: IQR=interquartile range, SCI=spinal cord injury, RIMT=resistive inspiratory muscle training.

Table 2. Descriptive data of cough capacity (PCF), respiratory muscle strength (MIP and MEP) and time-dependent confounders

	T0, n=40	T1, n=40	T2, n=36	T3, n=29
PCF in l/sec, mean ± SD	5.1 ± 1.8	5.8 ± 2.0	5.8 ± 1.9	6.6 ± 1.9
MIP in cm H_2O, mean ± SD	56.2 ± 26.2	76.4 ± 29.2	77.7 ± 26.7	93.7 ± 32.7
MEP in cm H_2O, mean ± SD	46.7 ± 26.4	57.8 ± 26.8	59.1 ± 28.6	67.4 ± 32.2
Body Mass Index in kg/cm^2, mean ± SD	23.4 ± 3.9	23.70 ± 3.5	24.03 ± 3.3	25.3 ± 4.3
Passive mobility*, n (%)	20 (50.0)	16 (40.0)	13 (36.1)	10 (34.5)
Spasticity, median (IQR)	2.00 (0.3-4.0)	3.00 (1.0-4.0)	3.00 (2.0-5.0)	3.00 (0.5-4.0)

Abbreviations: PCF=peak cough flow, MIP=maximum inspiratory pressure, MEP=maximum expiratory pressure, IQR=interquartile range. *Passive mobility: with assistance or motorized wheelchair.

DISCUSSION

The results of the present study showed that both MIP and MEP were longitudinally associated with cough capacity in persons with SCI. The results of the basic models and the change models showed similar relationships. Therefore, we can conclude that associations were mainly based on within-subject variance. In other words, if persons are able to improve their respiratory muscle strength, cough capacity will also improve. To the best of our knowledge, longitudinal relationships between respiratory muscle strength and cough capacity in persons with SCI have not been studied before.

Table 3. The longitudinal association between respiratory muscle strength (MIP and MEP) and peak cough flow: GEE models with dependent variables and confounders

Variables	Model with MIP as independent variable			Model with MEP as independent variable		
	beta	SE	P	beta	SE	P
Constant	3.284	0.497	.000	2.848	1.263	.024
T0 – T1	0.125	0.197	.523	0.541	0.181	.003
T0 – T2	0.168	0.205	.412	0.567	0.204	.005
T0 – T3	0.122	0.245	.618	0.818	0.240	.001
MIP	0.032	0.006	.000	NE	NE	
MEP	NE	NE		0.015	0.005	.006
Confounders						
Smoking history, pack years	−0.007	0.010	.480	-	-	
Body mass index	-	-		0.065	0.055	.235

Outcomes are results of multivariable generalized estimating equation (GEE) analysis with unstandardized regression coefficients (beta) and their standard errors (SE). The regression coefficients represent the change in outcome associated with an increase in the independent variable of 1 unit; T0=4 weeks after the start of active inpatient rehabilitation; T1=9 weeks after T0; T2=17 weeks after T0; T3=one year after discharge inpatient rehabilitation; MIP=maximum inspiratory pressure; MEP=maximum expiratory pressure; NE=not entered.

Table 4. The longitudinal association between change in respiratory muscle strength (ΔMIP and ΔMEP) and the change in peak cough flow: change model

Variables	Model with ΔMIP as independent variable			Model with ΔMEP as independent variable		
	beta	SE	P	beta	SE	P
Constant	0.173	.116	.134	1.319	0.672	.050
ΔMIP	0.027	.008	.001	NE	NE	
ΔMEP	NE	NE		0.012	.007	.085
Confounders						
Smoking history, pack years	−0.006	.003	.023	-	-	
Body mass index	-	-		−0.036	.022	.095
Age	-	-		−0.003	.005	.591

Outcomes are results of multivariable generalized estimating equation (GEE) analysis with unstandardized regression coefficients (beta) and their standard errors (SE). The regression coefficients represent the change in outcome associated with an increase in the independent variable of 1 unit; T0=4 weeks after the start of active inpatient rehabilitation; T1=9 weeks after T0; T2=17 weeks after T0; T3=one year after discharge inpatient rehabilitation; ΔMIP=change in MIP, ΔMEP=change in MEP; NE=not entered.

In agreement with findings in previous cross-sectional studies on PCF, our results showed a stronger association with MIP than with MEP.[9, 10] This suggests that strong inspiratory muscles are important to produce an effective cough in persons with SCI. Inherent to their injury, persons with SCI typically have a larger loss of expiratory muscle function than inspiratory muscle function. Therefore, their cough largely depends on the function of the preserved inspiratory muscles, which are involved in the pre-cough inspiratory phase.[16] Pre-cough inspiration to high lung volumes optimizes expiratory pressures and enhances expiratory airflow during the expulsion phase of cough.[7] At large lung volumes the remaining expiratory muscles are near their optimal length to produce tension and the recoil pressure of the lungs and thorax is increased.[7] Therefore, strength training of the inspiratory muscles may enhance cough capacity in persons with SCI. Nevertheless, the RCT that was the basis of the current study, showed that RIMT led to improvement in inspiratory muscle strength but not in cough capacity.[11] The lack of an effect on cough capacity may have been caused by large differences in the course of respiratory function between individuals and a large (spontaneous) improvement in inspiratory strength in the control group.

Whether the association between respiratory muscle strength and cough is clinically relevant depends on the size of the association, the potential change, and to what extent someone's cough is affected. The afore-mentioned RCT showed an average improvement in MIP of 26 cm H_2O after 8 weeks of RIMT.[11] In accordance to the associations found in the present study this may lead to an average improvement of PCF with 0.70 l/sec (26 x 0.027). Furthermore, the present study showed that many persons with recent SCI have PCF's below normal or at the low end of cough flows in able-bodied persons (6 to 20 l/sec).[7] Moreover, several persons did not meet the minimal flow of 2.7 l/sec necessary to clear secretions (7 persons at T0, 4 at T1, and 2 at T2).[17] These persons are dependent on the availability of assistance and/or equipment to produce an effective cough. They are probably susceptible to develop pneumonia from a normally harmless cold. Therefore, we feel that - especially in the early phase after injury - even small improvements in cough capacity may be essential to decrease the risk of serious respiratory complications.

Because only persons with impaired pulmonary function were included, results cannot be generalized to the entire SCI-population. Nevertheless, persons with impaired pulmonary function are at greater risk of respiratory complications,[18] and therefore interventions to reduce the risk of respiratory complications should focus on this vulnerable group. In addition, this study was conducted in the first 18 months after injury. As lung tissue and ribcage are known to become progressively less compliant over the years, the relationship between respiratory muscle function and cough may be different in persons with chronic SCI.[19] The fact that we used data of an RCT could have influenced the results. Nevertheless, analysis showed that the group allocation had no influence, i.e. was not a confounder, on any of the longitudinal relationships found. Therefore, we believe it was legitimate to combine the data of both groups. Finally, PCF was determined during a voluntary cough maneuver; a maneuver dependent on effort and motivation.[20] Although all persons were encouraged vigorously during the cough-maneuvers, voluntary cough flow may still be lower than a spontaneous reflex-based cough. This may have affected the results of this study.

In conclusion, results of the present study indicate that improvement of respiratory muscle strength may lead to improvement in cough capacity in persons with SCI who have impaired pulmonary function. Particularly, training of the inspiratory muscles may be a good strategy to enhance cough in the absence of expiratory muscle function. Whether this results in lower morbidity, hospitalization and death due to respiratory complications needs to be addressed in future research. In addition, further research is necessary to study relationships between respiratory function and cough in chronic SCI.

SUPPLIERS

a. Oxycon Delta®: CareFusion, Leibnizstrasse 7, 97204 Hoechberg, Germany
b. MicroRPM®: CareFusion UK 232 Ltd., The Crescent, Jays Close, Basingstoke RG22 4BS U.K.

ACKNOWLEDGEMENTS

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Chapter **7**

General discussion

In this thesis we aimed to gain insight into respiratory function in the first years after spinal cord injury (SCI). We studied respiratory function, changes over time, consequences of impaired respiratory function and the effects of an added respiratory training program.

MAIN FINDINGS

For the first part of this thesis (Chapter 2, 3, and 4) we used data of a Dutch multicenter prospective cohort study (the Umbrella and SPIQUE project). We found that parameters of pulmonary function at discharge from inpatient rehabilitation can be used as predictors for respiratory infection in the first year after discharge (Chapter 2). In Chapter 3, we studied the course of pulmonary function. Forced vital capacity (FVC) improved on average 5.1% between discharge from inpatient rehabilitation and the 5 years thereafter. However, the inter-individual differences in change were large and many persons showed a decline of FVC (in 14.9% of persons during the first year and in 28.3% during the 4 years thereafter). The decline in FVC during the first year after inpatient rehabilitation was associated with higher body mass index (BMI), lower inspiratory muscle strength, and declined physical fitness. In Chapter 4, we focused on respiratory function and respiratory infections 5 years after discharge. We found that a considerable proportion of the study population had impaired pulmonary function, impaired perceived cough strength, dyspnea at rest, and dyspnea during physical activity. In addition, the incidence of respiratory infection was high compared to the general population. Pulmonary function was associated with limitations in social functioning but not with other domains of health-related quality of life (HRQOL) or dyspnea. Persons with dyspnea experienced lower social functioning, general health, mental health and vitality. For the second part of the thesis (Chapter 5 and 6) we conducted a multicenter randomized clinical trial (RCT) on the effects of resistive inspiratory muscle training (RIMT). We assessed immediate and long-term effects of RIMT added to the usual inpatient rehabilitation care in persons with recent SCI who had impaired pulmonary function (Chapter 5). RIMT had a positive immediate effect on inspiratory muscle strength, but at follow-up this effect did not sustain. Except for an immediate effect on mental health, we found no effect on other measures of respiratory function, HRQOL or respiratory complications. Finally, we investigated the longitudinal relationship between respiratory muscle strength and cough capacity in more detail (chapter 6). This study revealed a positive association between respiratory muscle strength and cough capacity. The associations found in this thesis are presented in Figure 1.

RESPIRATORY COMPLICATIONS

Survival rates and medical care following SCI have improved largely over the last decades and have resulted in a decline of mortality during the first 2 years after injury.[1] However, mortality rates in the period thereafter have not changed substantially, and respiratory diseases, particularly lower tract respiratory infections, remain a major cause of death and hospitalization in persons with chronic SCI.[2-5] To date, mortality in SCI is still up to three times higher than in the general population.[6] Even in countries with

a relatively high standard of medical care, such as The Netherlands, mortality rates remain high. In fact, 12% of persons from the Dutch prospective cohort studied in this thesis died during a mean follow up of 6.2 years (standardized mortality rate 5.3).[7] Thirty percent of the mortality cases in this cohort was caused by respiratory diseases.
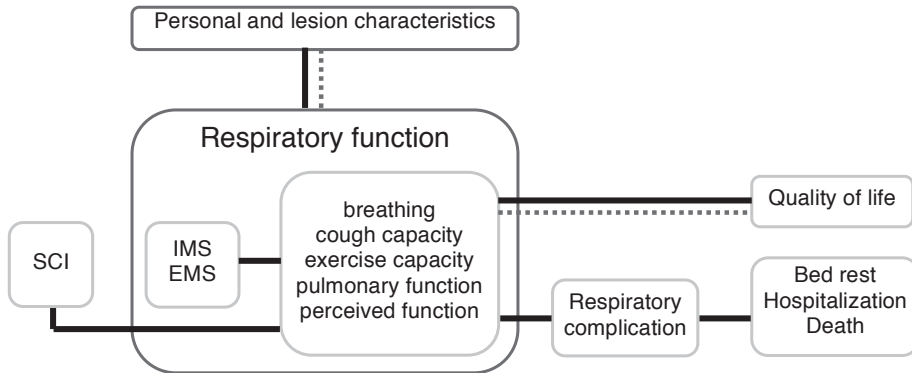
Figure 1. Schematic representation of associations studied in this thesis. The solid lines represent a significant association, whereas the dotted lines represent associations that were studied but not found. Abbreviations: SCI=spinal cord injury, IMS=inspiratory muscle strength, EMS=expiratory muscle strength

Incidence of respiratory infections

In this thesis, we studied the incidence of respiratory infection in the first and fifth year after discharge of inpatient rehabilitation. Physicians determined retrospectively, using a questionnaire on medical complications, whether participants had had a respiratory infection. These infections were defined as 'clinically important' infections, not simple nose or head colds. In our studies (Chapter 2 and 4) we found that in the survivors of the Dutch cohort 10.0% suffered from respiratory infection during the first, and 8.9% during the fifth year after discharge from inpatient rehabilitation. These incidence rates are somewhat higher than those reported in other SCI populations.[8, 9] This difference is likely caused by differences in definition and measurement methods. For example, McKinley et al[8] only included radiographically confirmed pneumonia and found an incidence of 3.5% in the first years post injury. The incidence rates found in our studies are considerably higher than in the general Dutch population. In the Dutch population (all ages) the estimated incidence of lower tract respiratory infection in 2011 was 2.9%.[10] In accordance with previous SCI-studies, the incidence of hospitalization due to respiratory infection found in our studies (1.4% in the first and 3.7% in the fifth year after discharge) was approximately ten times higher than in the general population.[5, 10, 11]

Respiratory management

The high incidence of respiratory infection and hospitalization, together with the fact that respiratory diseases are a common cause of death following SCI, emphasizes the importance of prevention and adequate treatment of respiratory infection in the acute and chronic phase. Current practice of respiratory care during the early phase of rehabilitation mainly focuses on regaining independent breathing and preventing respiratory complications. Treatment involves weaning, de-cannulation, techniques to prevent aspiration, glossopharyngeal breathing, deep breathing exercises, coughing exercises, chest physiotherapy, assisted coughing techniques, positive airway pressure ventilation, positioning, mechanical insufflation, abdominal binders, and medication.[12, 13] These techniques are frequently utilized in the early phase after SCI. However, in a later phase when persons breathe independently and respiratory function appears to be stable, respiratory care tends to move to the background and consists mainly of responding to emergent respiratory complications such as infections. It may be possible, and from the perspective of the high hospitalization and mortality rates, necessary, to improve current practice. Adding specific interventions may result in greater improvement of respiratory function.[14, 15] Better outcome of initial rehabilitation may protect persons from respiratory complications in the years thereafter. In addition, better follow-up care may prevent unnecessary decline - caused by other factors than the initial neurological impairment - of respiratory function and entering a downward spiral with increasing risk of severe respiratory complications.

Identifying persons at risk

A first step into improving respiratory follow-up care is to identify persons at risk for complications. Persons with SCI who are neurologically the most impaired (i.e. those with complete high tetraplegia) are known to be at greatest risk of respiratory complications.[8, 16] However, the relationship between lesion characteristics and pulmonary function is not straightforward: respiratory complications are not only restricted to persons with complete tetraplegia and pulmonary function varies strongly within different lesion groups.[17, 18] In this thesis (Chapter 2), we showed that parameters of pulmonary function measured at discharge from inpatient rehabilitation can be used as predictors of respiratory infection in the first year thereafter. Forced expiratory volume in one second (FEV_1 in liters and % of the predicted value), FVC in liters, and peak expiratory flow (PEF in l/sec and % predicted) were all moderately accurate predictors. To explain the predictive characteristics of the parameters of pulmonary function we use FEV_1 (in liters). An FEV_1 with a cut-off point of 2.5 l has a good sensitivity and a good specificity in predicting respiratory infection. Also the positive predictive value is high, meaning that just over one-quarter (26.2%) of persons with an FEV_1 below 2.5 l actually experienced respiratory infection within one year after discharge. However, 21.4% of persons who experienced respiratory infection would have been missed. With a higher cut-off point fewer persons will be missed, but more persons will be falsely identified at risk. This knowledge can be used in the future to target more intensive follow-up care to persons at high risk.

RESPIRATORY FUNCTION AFTER INPATIENT REHABILITATION

Decline of pulmonary function

In this thesis (Chapter 3) we showed that the relatively large improvement of pulmonary function during inpatient rehabilitation (12.4% predicted FVC) continued to some extent (5.1%) in the 5 years thereafter. However, the change in pulmonary function differed largely between persons, and a considerable number of persons showed a larger than normal decline in pulmonary function; FVC declined in 14.9% during the first year and in 28.3% during the 4 years thereafter. This excessive decline in the early years after discharge is particularly worrisome with respect to the association between pulmonary function and respiratory infection as described above, and with respect to previously demonstrated associations between low pulmonary function and high mortality rates in abled-bodied and in persons with chronic SCI.[4, 19] A declining pulmonary function may cause a negative spiral of recurrent respiratory infection, increasing damage of lung tissue and ongoing decline of pulmonary function, which may eventually lead to respiratory failure or death.

Decline of pulmonary function in the first year after discharge was associated with several potentially modifiable factors: low inspiratory muscle strength (measured by maximal inspiratory pressure: MIP), high BMI, and a declined physical fitness. The same (but non-significant) patterns were found 5 years after discharge. Stolzmann et al[20] found similar factors (low MIP and an increase in BMI) in their study on persons with chronic SCI. Taking into account that many persons with SCI gain weight and become less active after inpatient rehabilitation,[21, 22] these findings suggest that adding both exercises to improve inspiratory muscle strength and treatment programs that aim at weight control and maintaining physical fitness after inpatient rehabilitation may prevent decline of pulmonary function.

Not solely a problem for complete tetraplegia

In contrast to what is often believed, respiratory problems are not solely a problem of persons with complete tetraplegia. In this thesis we found that low pulmonary function, dyspnea, weak cough capacity, and respiratory infections were more common in persons with complete tetraplegia, but also present in persons with less severe neurological deficits. In addition, even though absolute values of pulmonary function were lower in persons with complete tetraplegia, excessive decline of pulmonary function did not depend on lesion level or completeness. Therefore, respiratory care after inpatient rehabilitation should not only focus on persons with complete tetraplegia, but on all persons who have impaired respiratory function.

Awareness of respiratory problems

In this thesis we found a weak association between FVC and perceived cough strength and no association between FVC and dyspnea (Chapter 4). This lack of a strong relationship between objectively measured respiratory function and perceived respiratory function is possibly one of the reasons that declining respiratory function goes unnoticed. Motor impairments due to paralysis may prevent persons with SCI

from being physically active and, as a result from challenging their respiratory system.[23] In addition, persons with SCI may become accustomed to their limitations and do not refer to respiratory impairments as a problem.[24] The discrepancy between objectively measured and perceived respiratory function is possibly also the basis of our clinical experience that persons with chronic SCI hardly ever spontaneously express treatment demands concerning respiratory function, despite having a low objectively measured pulmonary function. One of the challenges of adequate respiratory care in chronic SCI may lie in the fact that persons with SCI seem to have limited awareness of existing respiratory function impairments. As long as persons are not aware of their impaired (declining) respiratory function, they may not seek medical care when necessary. Early signs of respiratory infection may be neglected and respiratory care may start too late, leading to preventable medical risks. Perhaps, in respiratory care a demand-driven approach (care based on felt need), as is currently promoted, is not optimal.[25]

Consequences for health-related quality of life

In addition to respiratory complications, impaired respiratory function may also have direct or indirect consequences on one's life in general or HRQOL. Associations between pulmonary function and the physical component of HRQOL, and between dyspnea and both physical and mental components of HRQOL were demonstrated in large population studies.[26, 27] The effects of respiratory function on HRQOL may not be strong, as HRQOL is a complex concept that depends on many sociodemographic, psychosocial, medical, and disability-related variables.[28-30] However, enhancing HRQOL is an important goal in the treatment of persons with SCI, and therefore knowledge about associations between respiratory function and HRQOL is of clinical relevancy.[31]

In this thesis (Chapter 4) we found several associations between parameters of respiratory function and domains of HRQOL. When corrected for lesion level and completeness, more limitations in social functioning were reported by persons with lower FVC, and persons who had severely impaired perceived cough strength and severe dyspnea. In addition, persons with dyspnea reported lower general health, mental health and vitality. As expected, these associations were not strong and parameters of respiratory function only contributed a small part of the explained variance of HRQOL. Although interpretation of these results have to be done with caution due to the cross-sectional nature of the study, these results appear to support the hypothesis that impaired respiratory function negatively affects HRQOL.

RESISTIVE INSPIRATORY MUSCLE TRAINING

The results of the RCT we conducted to study the effects of RIMT (Chapter 5) are schematically presented in Figure 2. Our results in combination with the results of a recently published RCT on RIMT and a meta-analysis on respiratory muscle training in general, provide sufficient evidence for the immediate positive effect of RIMT on inspiratory muscle strength in persons with recent SCI.[14, 32] We found a significant immediate effect of RIMT on MIP (11.7 cm H_2O) which was comparable with the pooled effect of the before mentioned meta-analysis (10.7 cm H_2O),[15] but lower than the effect found by Mueller et al[32] (26.5

cm H_2O). When considering the relative improvements in the RIMT groups, the results were quite similar (46.6% in our study versus 53.6% in the study of Mueller et al.) despite lower training intensities in our study (50% to 70% of baseline MIP versus 80% of actual MIP).

The positive immediate effect on MIP found in our study sustained partly but was no longer statistically significant at follow-up. Post-hoc analyses revealed that a large part of the sustained effect after 8 weeks of the intervention, seemed to be caused by the eight persons who continued RIMT after the intervention period. This finding suggests that a longer training period may prolong the effect of RIMT on MIP. Therefore, for long-term effects maintenance training may be needed as previously reported in persons with COPD.[33]
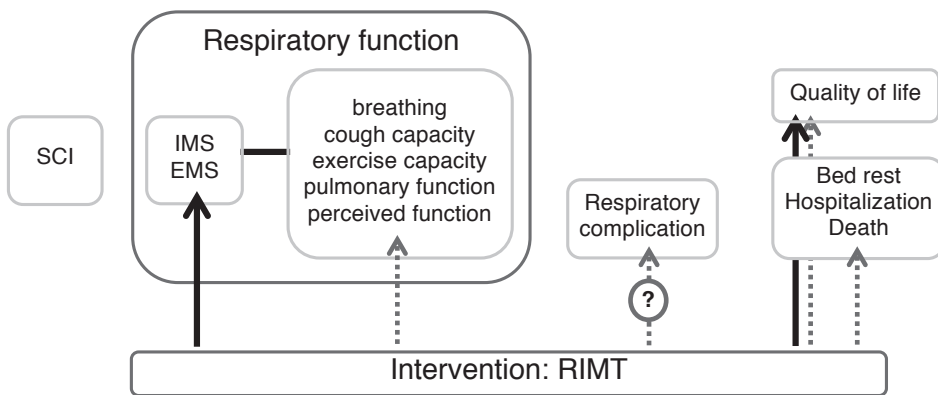
Figure 2. Schematic representation of effects of RIMT and changes in respiratory muscle function. The solid lines represent a significant association, whereas the dotted lines represent associations studied but not found. Abbreviations: SCI=spinal cord injury, IMS=inspiratory muscle strength, EMS=expiratory muscle strength.

Who benefits most?

Changes in MIP over time varied considerably between persons, both in the intervention and the control group. Within the intervention group these differences may be explained by the degree to which persons respond to the intervention. Previous meta-analyses in persons with heart failure[34] and in persons with COPD[35] showed that persons with low MIP at baseline responded better to RIMT than others. In our study we found no indication (unreported post-hoc analyses) for differences in effect between persons with low MIP at baseline (below 60 cm H_2O) and persons with higher MIP. Neither did we find differences in effect between lesion group (tetra AB or others) and cause of SCI (traumatic or not). However, our RIMT-group might have been too small for valid conclusions about this topic. Future studies with larger sample sizes are needed to assess who responds best.

In all persons (RIMT group and control group) changes in MIP over time may vary due to differences in spontaneous recovery. It was demonstrated previously that inspiratory muscle strength improves during regular inpatient rehabilitation and the year after.[36] Spontaneous recovery may mask the added

intervention effect. In addition, other factors such as concomitant trauma of lung tissue and thorax, secondary medical complications, development of spasticity in the trunk muscles, and differences in activity level may affect the course of recovery. Here again, the number of patients included in the RCT does not allow additional analyses with firm conclusions.

The importance of inspiratory muscle strength

In the interpretation of the data, the difference between the size of treatment effect and the relevance of the effect must be considered. It may be that persons with marked inspiratory muscles weakness are at the greatest need for improved inspiratory muscle strength, and a relatively small increase in this subgroup is probably clinically more relevant than a large improvement in the subgroup that is characterized by relatively stronger inspiratory muscle strength.

Persons with marked inspiratory muscle weakness are at risk of hypoventilation, fatigue of inspiratory muscles and respiratory pump failure. In normal situations only little inspiratory force (5-10 cm H_2O) is needed to establish quiet breathing. However, in situations of increased respiratory demand (during exercise, the strenuous work of wheelchair propulsion and transfers, and during periods of illness) higher forces are needed.[23, 37] Particularly during episodes of severe illness (fever, sputum retention, respiratory infection, and cor pulmonale) the normally sufficient inspiratory muscle strength may suddenly be insufficient. Increased breathing frequency and a low reserve capacity of the inspiratory muscles can lead to fatigue of the inspiratory muscles and may eventually lead to respiratory failure.[23, 38, 39] Inspiratory muscle strength may also become insufficient if the load against which the respiratory pump must operate is increased.[37] The load is increased when lung compliance becomes low (due to atelectasis) and/or the chest wall becomes stiff (due to lack of regular deep inspiration).[40] In addition, upper airway obstruction (as in sleep disturbed breathing) may increase the load.[37]

Effect of RIMT and improved MIP on other outcome measures

Although we found an effect of RIMT on inspiratory muscle strength, we found no effect on other measures of respiratory function, HRQOL, and respiratory complications (Figure 2). The only exception was a positive immediate effect on mental health which may have been caused by the extra attention given to persons who performed RIMT. The lack of an effect on respiratory complications should be interpreted with caution because the study was underpowered for this outcome measure. To attain better insight into the effect of respiratory muscle training on long-term respiratory complications, large-scale studies with a long (several years) follow-up time are necessary.

Relationship between respiratory muscle strength and cough capacity

Besides the effect of RIMT on inspiratory muscle strength, effects on lung volumes and cough capacity were most expected, e.g. based on our own study (chapter 3 of this thesis) and the studies of Tamplin et al[14] and Kang et al[41] However, these effects were not found. This may be the result of a too small improvement of inspiratory muscle strength, spontaneous recovery, heterogeneity and selection criteria

(composition) of the study group. Despite the fact that no effects were found on these measures, a longitudinal relationship was found between inspiratory muscle strength and cough capacity and between expiratory muscle strength and cough capacity (Chapter 6). After correction for confounders, a 10 cm H_2O higher MIP was associated with a 0.32 l/sec higher PCF, and a 10 cm H_2O higher maximum expiratory pressure (MEP) was associated with a 0.15 l/sec higher PCF. The associations found were mainly based on within-subject variation, which means that if persons are able to improve their respiratory muscle strength, cough capacity will also improve. Improvement of cough capacity in persons with SCI may be essential to decrease the risk of serious respiratory complications. Many persons with recent SCI have an extremely low cough capacity, which makes them dependent on the availability of assistance and/or equipment to produce an effective cough and as a result susceptible to develop pneumonia from a normally harmless cold.[42]

GENERALIZABILITY OF RESULTS

The results of this thesis cannot be generalized to all persons with SCI. Persons with breathing support or tracheostomy were not included and are likely to cope with additional medical issues. Furthermore, the results are based on persons admitted to rehabilitation centers of the Netherlands. In the Netherlands, medical and rehabilitation care is well organized. Acute and rehabilitation care is available for all inhabitants and the duration of rehabilitation tends to be longer than in many other countries.[43] Therefore, participants in our study may have had a better chance to optimize their pulmonary function before leaving the rehabilitation center. This may account for the relatively high pulmonary function values found in this thesis.

CLINICAL IMPLICATIONS

The results of this thesis show that persons with SCI, their caregivers, and professionals, should be aware of an increased risk for impaired respiratory function, excessive decline of pulmonary function, and respiratory infection in the early years after initial rehabilitation. People should realize that these respiratory threats are not exclusive for persons with complete tetraplegia and may go undetected for some time. Waiting for persons to present themselves with symptoms such as dyspnea is not sufficient. Based on our results we believe that regular monitoring of pulmonary function after inpatient rehabilitation is important in all persons with SCI. Monitoring pulmonary function ensures timely detection of excessive decline of pulmonary function and can identify persons at risk for respiratory infection. Once persons at risk are identified, it becomes possible to apply strategies to prevent respiratory complications. Furthermore, exercises to improve inspiratory muscle strength and adding treatment programs that aim at weight control and maintaining fitness after inpatient rehabilitation may be beneficial to prevent decline of pulmonary function. Finally, there is sufficient evidence for the positive effect of RIMT

on inspiratory muscle strength in recent SCI. Therefore RIMT should become part of standard respiratory care in persons with marked inspiratory muscle weakness during initial SCI rehabilitation.

FUTURE RESEARCH

This thesis was a first step in identifying persons at risk of declining pulmonary function and respiratory complications in the years after inpatient rehabilitation. Further research is necessary to confirm these results in a larger population. In addition, research is needed to find predictors in the more chronic phase after inpatient rehabilitation. Furthermore, treatment programs that aim to prevent excessive decline of pulmonary function and respiratory complications should be developed, implemented, and evaluated.

Future research is needed to attain better insight in the underlying mechanisms of respiratory muscle training and the effect on respiratory complications. In addition, there is a great need to find treatment strategies that can restore lung volumes in chronic SCI. A combination of existing techniques such as respiratory muscle training, mechanical insufflation (or air stacking) and abdominal binders may have the potential to accomplish this goal.
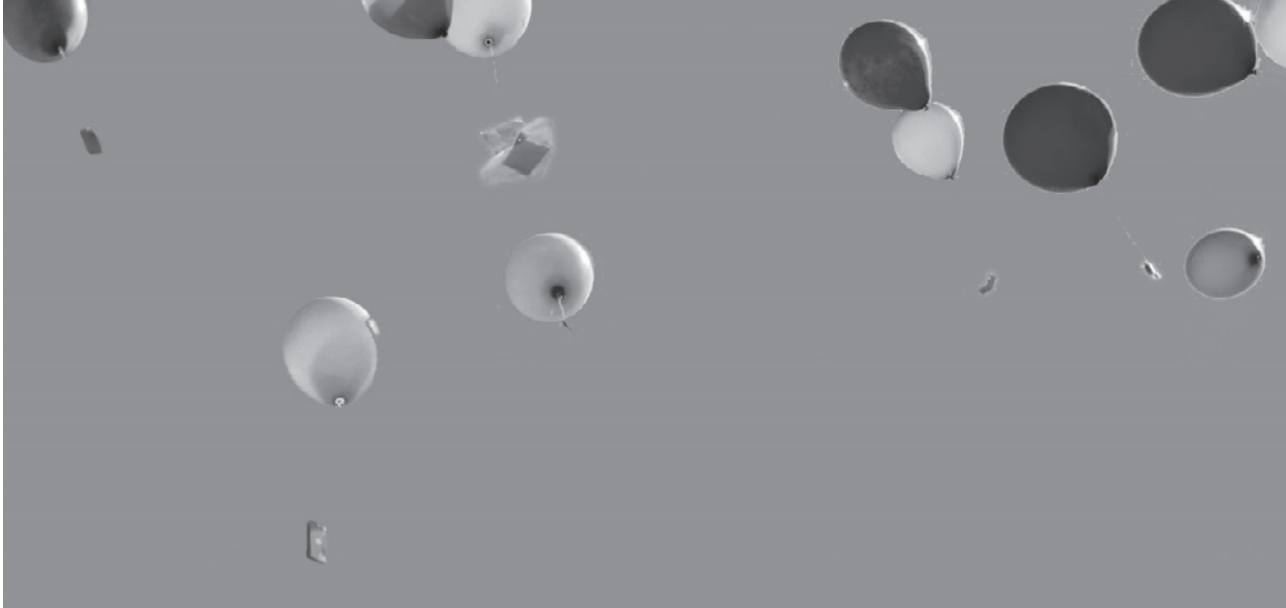
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Summary

Survival rates and medical care following spinal cord injury (SCI) have improved largely over the last decades and have resulted in a decline of mortality during the first 2 years after injury. The mortality rates in the period thereafter have not changed substantially. Respiratory diseases, particularly lower tract respiratory infections, remain a common cause of early death and hospitalization in persons with chronic SCI. Therefore, in this thesis we focused on respiratory function after SCI. We studied changes in respiratory function, the prevalence of impaired respiratory function and consequences in the early years after inpatient rehabilitation. In addition, we studied the effects of a specific respiratory training program added to the usual inpatient rehabilitation treatment. For the first part of this thesis we used data of a Dutch multicenter prospective cohort study (the Umbrella and SPIQUE project). For the second part we conducted a multicenter randomized controlled trial (RCT) on the effects of resistive inspiratory muscle training (RIMT).

The introductory **Chapter 1** describes background information concerning SCI, respiratory function, the effects of SCI on respiratory function, consequences of impaired respiratory function, and current respiratory management. In this chapter, a schematic representation of the assumed relationships between spinal cord injury, respiratory function and the consequences for general functioning are shown. A short description of the Umbrella and SPIQUE project is provided. The chapter concludes with the aims and outline of this thesis.

The aim of the study, described in **Chapter 2**, was to find a method to identify persons at risk for respiratory infection after inpatient rehabilitation. We studied whether parameters of pulmonary function measured at discharge could predict respiratory infections in the first year after discharge of inpatient rehabilitation. Both forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF) were significantly lower in persons who had had respiratory infection than in those who did not. With exception of FVC in percentage predicted, all parameters were moderately accurate predictors of respiratory infection in the first year after discharge of inpatient rehabilitation.

Chapter 3 concerns the study focused on changes in pulmonary function during the first 5 years after inpatient rehabilitation. We found that FVC increased 5.1% over that period. Although persons with complete tetraplegia had a significantly lower absolute pulmonary function than those with incomplete tetraplegia or persons with paraplegia, the changes over time were not different. However, changes in pulmonary function differed largely between persons. During the first year after inpatient rehabilitation, FVC declined in 14.9% of the persons (beyond the normal age-related decline). During the four years thereafter, FVC declined in 28.3% of the persons. We found several potentially modifiable determinants of declined FVC in the first year: low inspiratory muscle strength, high body mass index, declined peak power output, and declined peak oxygen uptake. Similar, but non-significant, patterns were observed for the period between one and five years after discharge.

Chapter 4 addresses the prevalence of impaired respiratory function, the incidence of respiratory infections and associations between respiratory function and health-related quality of life (HRQOL), 5 years after inpatient rehabilitation. Pulmonary function was impaired (FVC below 80% predicted) in 30.9% of
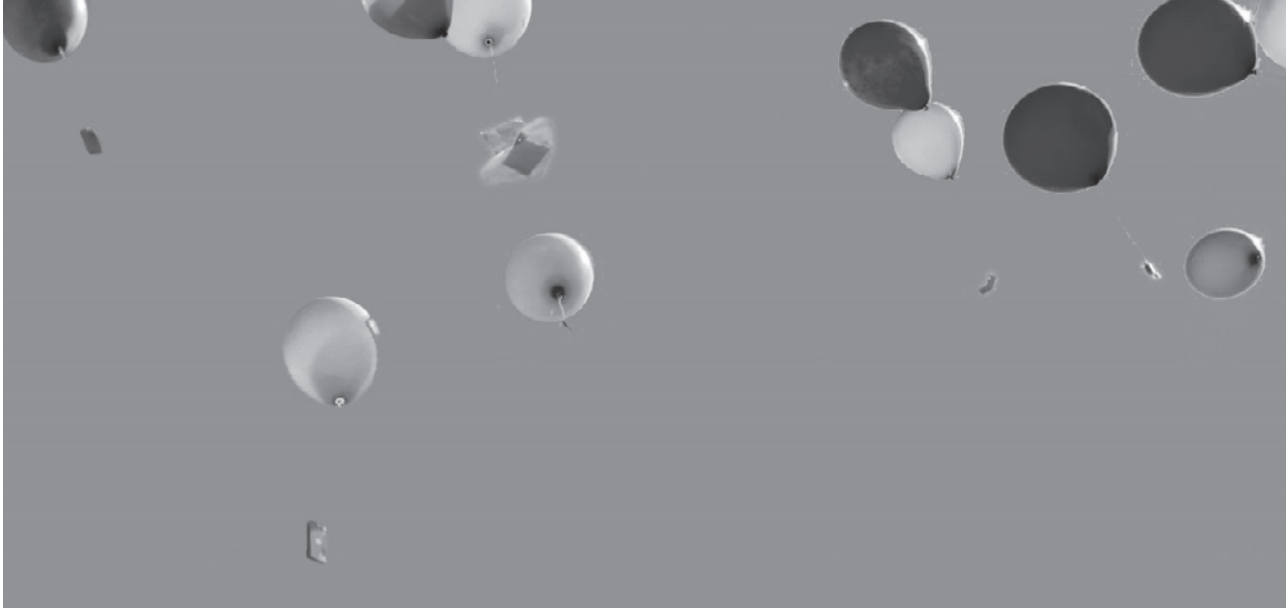
the persons, 35.9% had impaired perceived cough strength, 18.4% experienced dyspnea at rest, and 29.0% experienced dyspnea during physical activities. Nine percent had had a respiratory infection in the year prior to the measurements. Furthermore, this study showed that FVC, impaired perceived cough strength and dyspnea were associated with social functioning. Dyspnea was also associated with other domains of quality of life (general health, mental health and vitality). More seriously impaired respiratory function was associated with lower quality of life.

In **Chapter 5** we describe the results of our RCT concerning the effects of RIMT. The immediate and long-term effects of RIMT on respiratory function, respiratory complications, and HRQOL in persons with recent SCI who had impaired pulmonary function were assessed. Forty persons were included and randomized to the intervention or the control group. All persons received usual rehabilitation care. Additionally, persons in the intervention group trained 5 times a week for 8 weeks with a RIMT-threshold trainer. This training had a positive effect on the maximum inspiratory pressure (MIP), a measure of inspiratory muscle strength, immediately after the training period. At follow-up this effect was no longer significant. With exception of an immediate effect on mental health, we found no effects on other parameters of respiratory function, respiratory complications, or HRQOL. The results concerning respiratory complications should be interpreted with caution as the sample size for this outcome may have been too small.

In **Chapter 6** we describe our study on longitudinal relationships between respiratory muscle strength and cough capacity. For this study we used data of the RCT described in chapter 5. We found that both MIP and maximum expiratory pressure (MEP) were significantly positively associated with peak cough flow (PCF). A 10 cm H_2O higher MIP was associated with a 0.32 l/sec higher PCF. A 10 cm H_2O higher MEP was associated with a 0.15 l/sec higher PCF. The association between MIP/MEP and PCF was mainly based on within-subject variance, indicating that improvement of respiratory muscle strength may lead to improvement in cough capacity in persons with SCI.

Finally, in **Chapter 7** we describe the main findings of this thesis. Then we discuss the risks of complications, respiratory management and the consequences of impaired or declining respiratory function. We discuss the need for better follow-up care to prevent respiratory complications. Furthermore, we discuss the effects of RIMT, which persons benefit most, and the importance of sufficient inspiratory muscle strength. Finally, we address clinical implications and make recommendations for future research.

Samenvatting

De overlevingskans en medische zorg na een dwarslaesie zijn sterk verbeterd in de afgelopen decennia en hebben geleid tot een daling van de sterfte in de eerste 2 jaar na het ontstaan van de dwarslaesie. De sterftecijfers in de periode daarna zijn echter vrijwel gelijk gebleven. Ziekten van de ademhalings-wegen, in het bijzonder infecties van de onderste luchtwegen, blijven een veel voorkomende oorzaak van vroegtijdig overlijden en ziekenhuisopnames bij mensen met een chronische dwarslaesie. Daarom richtten wij ons in dit proefschrift op de ademhalingsfunctie bij mensen met een dwarslaesie. Wij bestudeerden het beloop van de longfunctie, het voorkomen van een beperkte ademhalingsfunctie en de gevolgen daarvan in de eerste jaren na de klinische revalidatie. Daarnaast onderzochten we de effecten van een trainingsprogramma gericht op de kracht van de inademingsspieren (resistive inspiratory muscle training: RIMT). Voor het eerste deel van dit proefschrift (**hoofdstuk 2, 3** en **4**) gebruikten we gegevens van een Nederlands multicenter prospectieve cohort onderzoek (het Koepel- en SPIQUE project). Voor het tweede deel (**hoofdstuk 5** en **6**) gebruikten we gegevens van een door ons opgezet multicenter effectstudie (randomized controlled trial: RCT) naar het effect van RIMT.

In **hoofdstuk 1** worden in het kort de gevolgen van een dwarslaesie beschreven. Vervolgens gaan we in op het effect van een dwarslaesie op de ademhaling, de gevolgen van een verminderde ademha-lingsfunctie en het huidige behandelbeleid. In dit hoofdstuk staat een model waarin de veronderstelde relaties tussen de dwarslaesie, de ademhalingsfunctie en de gevolgen voor het algemeen functioneren zijn weergegeven. Er wordt een korte omschrijving van de opzet van het Koepel- en SPIQUE project gegeven. Het hoofdstuk eindigt met de doelen en de opzet van dit proefschrift.

Het doel van het onderzoek dat in **hoofdstuk 2** staat beschreven, was om een methode te vinden om personen met een hoger risico op luchtweginfecties na ontslag uit de klinische revalidatiesetting te identificeren. We onderzochten of verschillende maten van longfunctie gemeten vlak voor het ontslag voorspellend waren voor het ontstaan van een luchtweginfectie in het eerste jaar na ontslag uit het revali-datiecentrum. Zowel geforceerde vitale capaciteit (FVC), geforceerd expiratoir volume in de eerste seconde (FEV$_1$) als expiratoire piekstroom (PEF) waren significant lager bij de personen met een luchtweginfectie dan bij de personen zonder luchtweginfectie. Met uitzondering van FVC gemeten in % voorspelde waarde, waren alle longfunctiematen redelijk nauwkeurige voorspellers voor het ontstaan van luchtweginfecties in het eerste jaar na ontslag.

Hoofdstuk 3 betreft het onderzoek gericht op het beloop van de longfunctie gedurende de eerste 5 jaar na de klinische revalidatie. Het bleek dat FVC in die periode nog 5,1% toenam. Hoewel personen met een complete tetraplegie een significant lagere absolute longfunctie hadden dan personen met een incomplete tetraplegie of personen met een paraplegie, was het beloop niet anders. Wel waren er grote verschillen in beloop tussen personen. In het eerste jaar na de klinische revalidatie ging 14,9% van de personen achteruit (meer dan de normale leeftijd gerelateerde achteruitgang) en in de vier jaar daarna 28,3%. We vonden een aantal potentieel beïnvloedbare determinanten van een afgenomen FVC in het eerste jaar: lage inademingskracht, een hoge body mass index, en een afname van het piek in-

spanningsvermogen en de piek zuurstofopname. Vergelijkbare, maar niet significante, patronen werden gevonden voor de periode van één tot vijf jaar na de revalidatie.
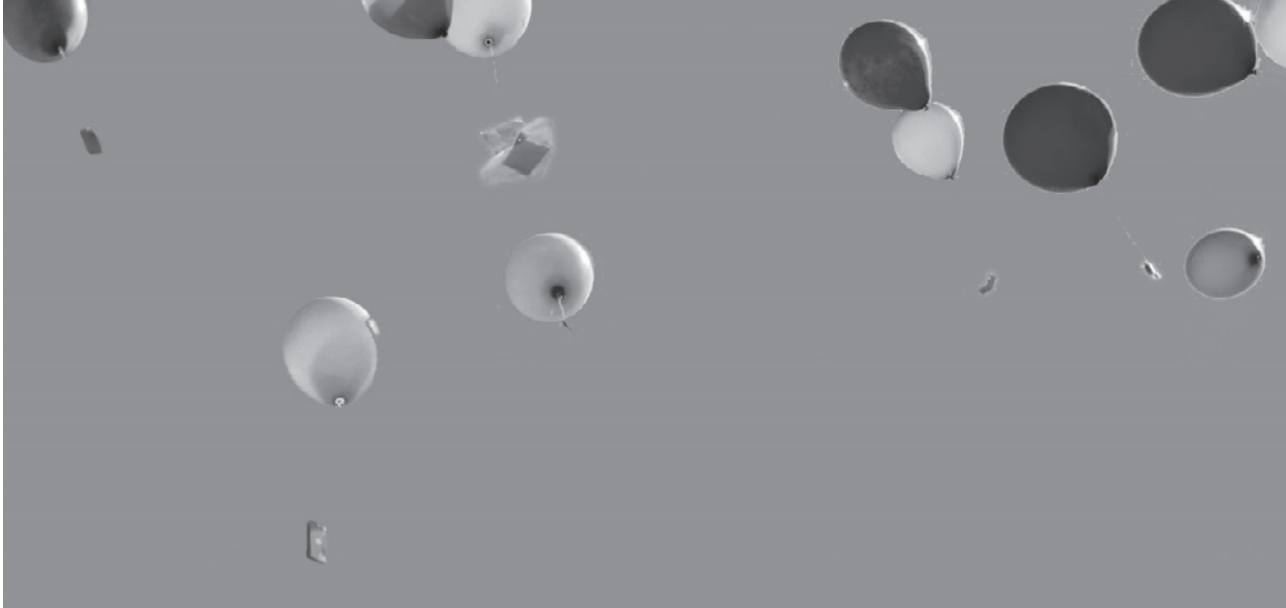
Hoofdstuk 4 behandelt de prevalentie van een beperkte ademhalingsfunctie, de incidentie van lucht-weginfecties en associaties tussen ademhalingsfunctie en gezondheid gerelateerde kwaliteit van leven, 5 jaar na de klinische revalidatie. De longfunctie was bij 30,9% van de personen aangedaan (FVC lager dan 80% voorspeld), 35,9% hadden een verminderde ervaren hoestkracht, 18,4% waren kortademig in rust en 29,0% waren kortademig tijdens lichamelijke activiteiten. Negen procent leed aan een luchtweginfectie in het jaar voorafgaande aan de meting. Verder toonde dit onderzoek aan dat FVC, ervaren hoestkracht en kortademigheid geassocieerd waren met sociaal functioneren. Kortademigheid was bovendien geassocieerd met andere domeinen van kwaliteit van leven (algemene gezondheid, mentale gezondheid en vitaliteit). Ernstiger verminderde ademhalingsfunctie was geassocieerd met lagere kwaliteit van leven.

In **hoofdstuk 5** beschrijven we de resultaten van de RCT naar de effecten van RIMT. De korte- en lange termijn effecten van RIMT op de ademhalingsfunctie, complicaties en kwaliteit van leven bij personen met een recente dwarslaesie en een beperkte longfunctie werden onderzocht. Veertig personen werden geïncludeerd en gerandomiseerd over een interventie- en een controlegroep. Alle personen volgden de gebruikelijke revalidatiebehandeling. Daarnaast trainden de personen in de interventiegroep 5 keer per week gedurende 8 weken met een RIMT-threshold trainer. Deze training had een positief effect op de maximale inademingsmonddruk (MIP), een maat voor inademingskracht, direct na de trainingsperiode. Bij de vervolgmetingen was dit effect niet meer significant. Met uitzondering van een direct effect op de mentale gezondheid, vonden we geen effecten op andere maten van de ademhalingsfunctie, complicaties of kwaliteit van leven. De resultaten ten aanzien van complicaties moeten met de nodige voorzichtigheid worden geïnterpreteerd, omdat de studiegroep voor deze uitkomstmaat mogelijk te klein was.

In **hoofdstuk 6** beschrijven we ons onderzoek naar longitudinale relaties tussen ademspierkracht en hoestcapaciteit. Voor dit onderzoek gebruikten we de gegevens van de in hoofdstuk 5 beschreven RCT. We vonden dat zowel MIP als maximale monddruk tijdens uitademen (MEP) significant positief geassocieerd waren met de piekstroom tijdens hoesten (PCF). Een 10 cm H_2O hogere MIP was geassocieerd met een 0,32 l/s hogere PCF. Een 10 cm H_2O hogere MEP was geassocieerd met een 0,15 l/s hogere PCF. De associatie tussen MIP/MEP en PCF was hoofdzakelijk gebaseerd op de binnen-persoonsvariantie. Dit suggereert dat verbetering van ademspierkracht kan leiden tot verbetering van de hoestcapaciteit bij mensen met een dwarslaesie.

Tenslotte, worden in **hoofdstuk 7** de belangrijkste bevindingen van dit proefschrift samengevat. Vervolgens bespreken we de risico's op complicaties, het behandelbeleid en de gevolgen van een be-perkte of afnemende ademhalingsfunctie. We bespreken de noodzaak van een betere nazorg teneinde complicaties te voorkomen. Verder bespreken we de gevonden effecten van RIMT, welke personen er het meeste baat bij hebben en het belang van voldoende inademingskracht. Tenslotte vertalen we de bevindingen van dit proefschrift in een aantal klinische boodschappen en doen we aanbevelingen voor toekomstig onderzoek.

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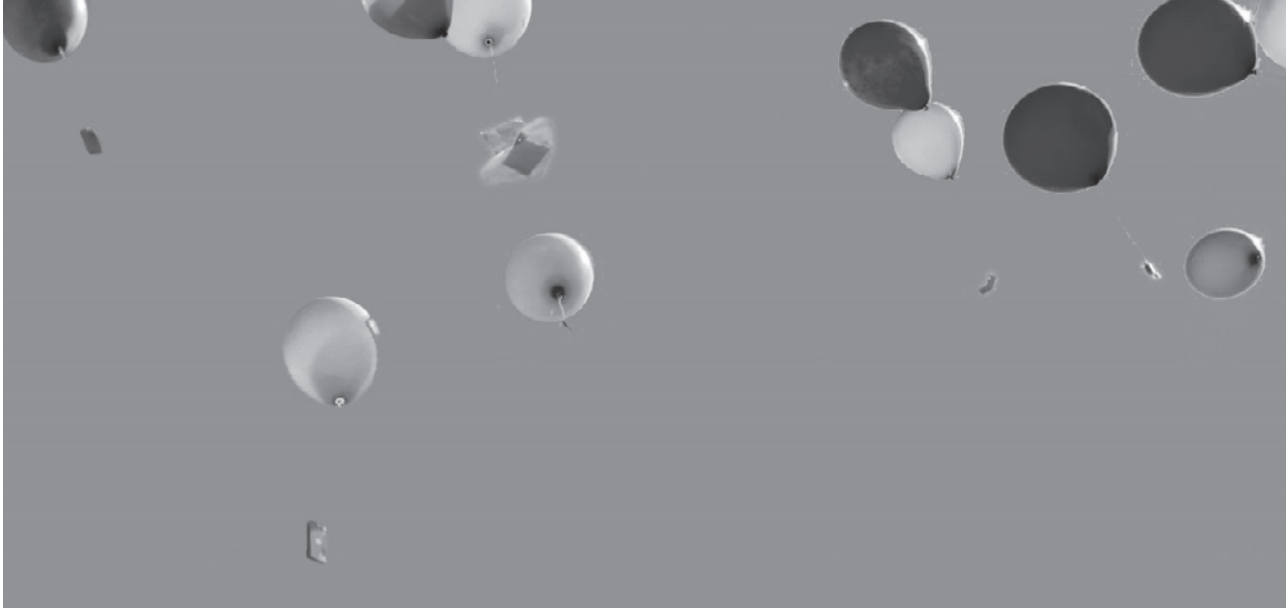
familie en vrienden

Paulus

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Dit proefschrift was nooit tot stand gekomen zonder de hulp van vele anderen. Met naam en toenaam wil ik Hans Bussmann bedanken voor zijn intensieve 'dagelijkse' begeleiding. Ook dank ik van harte de overige leden van het begeleidingsteam: Henk Stam, Janneke Haisma, Michael Bergen en Maria Hopman. En natuurlijk Luc van der Woude, die mij zowat 'dwong' om te gaan promoveren.

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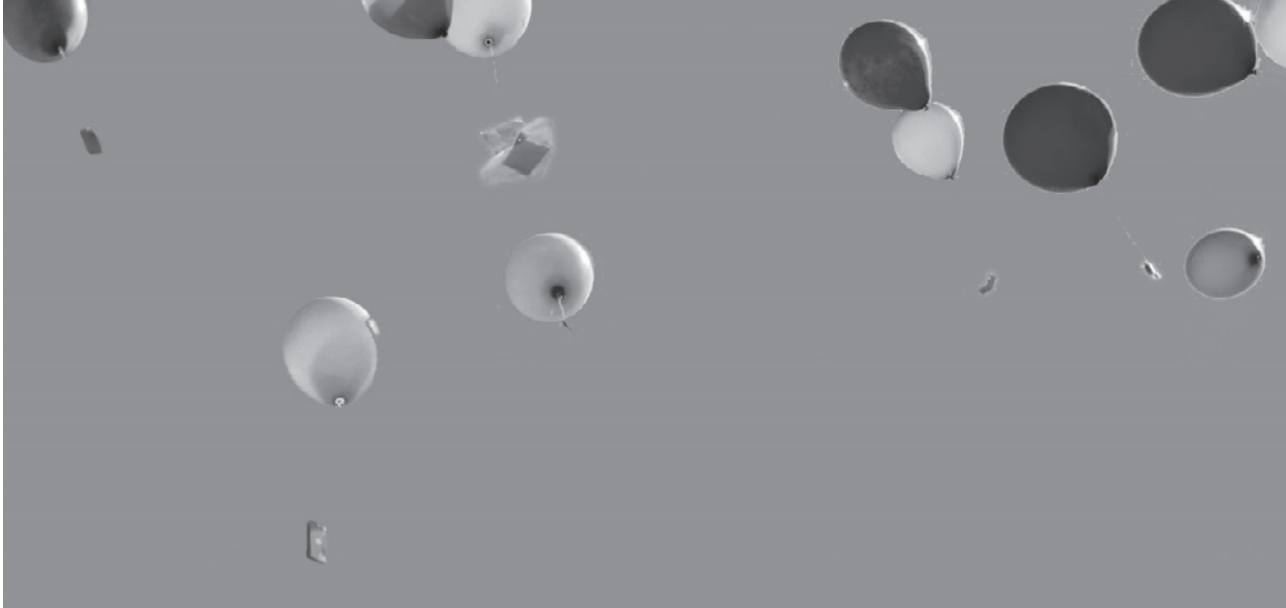
About the author

Karin Postma was born in Leiden on the 3rd of January 1964. She finished her secondary school (VWO) in Delft in 1981. In 1986 Karin completed her training as a physiotherapist in Leiden and started working in a nursing home. Three years later she pursued her wish to work in a rehabilitation setting and moved to Grand Rapids, Michigan (USA), where she worked at Mary Free Bed Hospital and Rehabilitation Center. In 1992 she moved back to the Netherlands and for some years she worked at several primary physiotherapy practices and rehabilitation centers. In 1995 Karin started her work at the newly opened Rijndam Rehabilitation Institute in Rotterdam. Alongside her work at Rijndam she studied Health Sciences with a major in Movement Sciences at Maastricht University. She obtained her master's degree in 2002. From 1999, she was also involved in the Dutch multicenter prospective SCI-cohort study as a research assistant. In October 2008 Karin started her PhD training at the Department of Rehabilitation Medicine of Erasmus MC University Medical Center Rotterdam. Currently, she continues her work at Rijndam as a physiotherapist at a department specialized in rehabilitation of people with spinal cord injury, multi-trauma, and amputation.

List of publications

Publications in international journals

Postma K, Berg-Emons HJ, Bussmann JB, Sluis TA, Bergen MP, Stam HJ. Validity of the detection of wheel-chair propulsion as measured with an Activity Monitor in patients with spinal cord injury. *Spinal Cord* 2005;43:550-7.

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van Langeveld SA, Post MW, van Asbeck FW, Ter Horst P, Leenders J, Postma K, Lindeman E. Reliability of a new classification system for mobility and self-care in spinal cord injury rehabilitation: the Spinal Cord Injury-Interventions Classification System. *Arch Phys Med Rehabil* 2009;90(7):1229-36.

Postma K, Bussmann JB, Haisma JA, van der Woude LH, Bergen MP, Stam HJ. Predicting respiratory infection one year after inpatient rehabilitation with pulmonary function measured at discharge in persons with spinal cord injury. *J Rehabil Med* 2009;41(9):729-33.

van Langeveld SA, Post, MW, van Asbeck FW, ter Horst P, Leenders J, Postma K, Rijken H, Lindeman E. Contents of physical therapy, occupational therapy, and sports therapy sessions for patients with a spinal cord injury in three Dutch rehabilitation centres. *Disabil Rehabil* 2010;33(5):412-22.

de Groot S, Post MW, Postma K, Sluis TA, van der Woude LH. Prospective analysis of body mass index during and up to 5 years after discharge from inpatient spinal cord injury rehabilitation. J Rehabil Med 2010;42(10):922-8.

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Postma K, Haisma JA, de Groot S, Hopman MT, Bergen MP, Stam HJ, Bussmann JB. Changes in pulmonary function during the early years after inpatient rehabilitation in persons with spinal cord injury: a prospective cohort study. *Arch Phys Med Rehabil* 2013;94(8):1540-6.

de Groot S, Postma K, van Vliet L, Timmermans R, Valent LJM. Mountain time trial in handcycling: exercise intensity and predictors of race time in people with spinal cord injury. *Spinal Cord* 2014;52(6):455-61.

Postma K, Haisma JA, Hopman MTE, Bergen MP, Stam HJ, Bussmann JB. Resistive inspiratory muscle training in people with spinal cord injury during inpatient rehabilitation; a randomized controlled trial. *Phys Ther* 2014. [Epub ahead of print]

Publications in Dutch journals

de Groot S, Dallmeijer A, Kilkens O, Post M, van Asbeck F, Nene A, Angenot E, Niezen A, Rijken H, Woldring F, Postma K, Bloemen J, Valent L, Van Langeveld S, Schuitenmaker M, van der Woude L. Onderzoek in de dwarslaesierevalidatie Beschrijving en belang van een multi-disciplinair multi-centrum prospectief cohort onderzoek. *Revalidata* 2005;27:5-13.

Van Langeveld SA, Post MWM, Van Asbeck FWA, Postma K, Leenders J, Pons K, Liefhebber HJ. Bruikbaar-heid van een classificatie van paramedische dwarslaesiebehandelingen. *Revalidata* 2007;135:20-4.

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Valent L, Gobets D, Holst L, van Vliet L, Postma K, de Groot S. Trainen voor de HandbikeBattle: effecten op fitheid en herstel. *Nederlands Tijdschrift voor Revalidatiegeneeskunde* 2014;3:99-103.
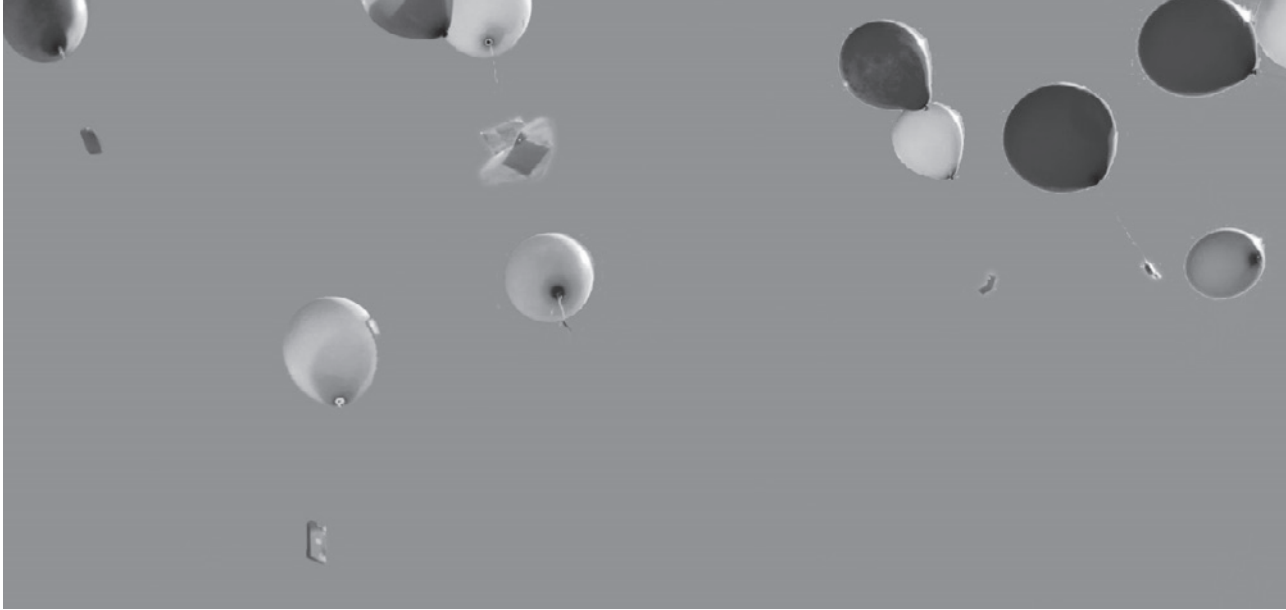
PhD portfolio

Summary of PhD training and teaching activities

Name PhD student: Karin Postma	**PhD period:** 2008 - 2014
Erasmus MC Department: Rehabilitation Medicine	**Promotor:** Prof.dr. H.J. Stam
Research School: None	**Supervisor:** Dr. J.B.J. Bussmann

1. PhD training

	Year	Workload (ECTS)
General academic skills		
Basiscursus regelgeving en organisatie voor klinisch onderzoekers (BROK), incl. certificaat GCP	2009	2.0
English Biomedical Writing and Communication	2010	4.0
Research Integrity	2013	2.0
Research skills		
Introduction to Data-analysis (NIHES: ESP03)	2009	1.0
Minicursus Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen	2009	0.2
Systematische Reviews en Meta-analyse, EMGO institute. Amsterdam	2009	1.0
Regression Analysis (NIHES: ESP09)	2010	1.9
Repeated Measurements (NIHES: CE08)	2012	1.4
Longitudinale data-analyse, EpidM. Amsterdam	2013	1.4
In-depth courses (e.g. Research school, Medical Training)		
Masterclass ´Ademspiertraining´, NPi, Papendal	2012	0.2
Oral Presentations		
'Respiratoire complicaties, longfunctie en inactiviteit bij personen met een dwarslaesie' at mini-symposium RCA. Amsterdam	2008	1.0
'Respiratoire complicaties, longfunctie en inactiviteit bij personen met een dwarslaesie' at the regional meeting for rehabilitation physicians. Rotterdam	2009	0.4
'Respiratory complications, pulmonary function and inactivity in SCI' at the dept of Rehabilitation Medicine Erasmus MC. Rotterdam	2009	0.4
'Inspiratory Muscle Training bij personen met een dwarslaesie' at Rijndam revalidatiecentrum. Rotterdam	2010	0.2
'Ademen, niet zo vanzelfsprekend …?' at Revalidatiecentrum De Hoogstraat. Utrecht.	2010	0.4
'Inspiratory Muscle Training bij personen met een dwarslaesie' at RCA. Amsterdam	2010	0.2
'Longfunctie en longproblematiek bij mensen met een dwarslaesie' at mini-symposium NVDG. Rotterdam	2010	1.0
'Respiratory infections and function 5 years after SCI rehabilitation' at the annual meeting of the ISCOS. Delhi, India	2010	1.0
'Decreased Respiratory function and consequences after SCI rehabilitation' at the PHD-day movement scientists. Rotterdam	2011	0.4
'Rijndam Racers to the top' at the dept. of Rehabilitation Medicine Erasmus MC. Rotterdam	2011	0.2
'Effectiviteit van Inspiratory Muscle Training tijdens de klinische revalidatie van personen met een dwarslaesie' at Heliomare. Wijk aan zee	2011	0.2

'Lung function in SCI up to 5 years after rehabilitation' at the annual meeting of the ISCOS. London, UK	2012	1.0
'Inspiratory muscle training bij mensen met een recente dwarslaesie' at mini-symposium NVDG. Nijmegen	2013	0.4
'Prevalence of Low Inspiratory Muscle Strength during inpatient rehabilitation' at the annual meeting of the ISCOS. Maastricht	2014	1.0
Poster Presentations		
'A challenge for persons with SCI; handcycling the Alpe d´Huez´ at the annual meeting of the ISCOS (2nd author). London, UK	2012	0.1
'Effect of Inspiratory Muscle Training during inpatient rehabilitation' at the annual meeting of the ISCOS. Istanbul, Turkey	2013	0.6
'Mountain time trial in handcycling: pilot study on exercise intensity and predictors of race time' at the 5th State-of-the-Art Congress (co-author). Groningen	2014	0.1
International conferences		
4th State-of-the-Art Congress RehabMOVE, Amsterdam	2009	0.9
ISCOS 2010, 49th annual scientific meeting of the international spinal cord society. Delhi, India	2010	0.9
ISCOS 2012, 51st annual scientific meeting of the international spinal cord society. London UK	2012	0.9
ISCOS 2013, 52nd annual scientific meeting of the international spinal cord society. Istanbul, Turkey	2013	0.9
5th State-of-the-Art Congress 'Rehabilitation: Mobility, Exercise & Sports'. Groningen	2014	0.9
ISCOS 2014, 53nd annual scientific meeting of the international spinal cord society. Maastricht	2014	0.9
Seminars and workshops		
NVDG mini-symposium	2008-2013	1.2
ISCOS post-conference workshop Physiotherapy. Delhi, India	2010	0.3
ISCOS pre-conference PT/OT workshop. Maastricht	2014	0.3
Didactic skills		
Other		
Research meetings dept. Rehabilitation Medicine Erasmus MC. Rotterdam	2008-2014	7.0
Review scientific articles for international journals	2010-2011	0.5
Developing E-learn SCI modules for ISCOS	2011-2012	1.2
2. Teaching activities		
Lecturing		
Basiscursus revalidatieartsen (AIOS training): 'trainen en meten van mobiliteit' at Rijndam revalidatiecentrum. Rotterdam	2008-2010	1.0
Minor teaching 2d year medical students. Rotterdam	2010-2014	1.0
ISCOS post-conference workshop: 'Respiratory management'. Delhi, India	2010	1.4
ISCOS post-conference workshop: 'Incorporating ICF into PT practice'. Delhi, India	2010	0.2
ISCOS pre-conference workshop: 'Respiratory management'. Maastricht	2014	1.2
Supervising practical's and excursions		
Supervising 2d year medical students with review assignments	2010	0.4
Supervising of movement technology students	2010	1.6

Instruction research assistants All Risk project	2011	0.2
Supervising of physical therapy student with minor project	2008	1.6
Supervising Master's theses		
Other		
Member of advisory team for the PhD project of S van Langenveld	2004-2010	2.4
Member of research committee of the HandbikeBattle	2013-2014	0.7
Member of organizing team PHD-day 2011	2011	0.1
Member of organizing team ISCOS pre-conference PT/OT workshop. Maastricht	2013/2014	0.6
Total		**52.0**