J Rehabil Med 2015; 47: 722–726

ORIGINAL REPORT

LONGITUDINAL ASSOCIATION BETWEEN RESPIRATORY MUSCLE STRENGTH AND COUGH CAPACITY IN PERSONS WITH SPINAL CORD INJURY: AN EXPLORATIVE ANALYSIS OF DATA FROM A RANDOMIZED CONTROLLED TRIAL

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Objective: **To assess the longitudinal association between respiratory muscle strength and cough capacity in persons with recent spinal cord injury.**
Design: **Longitudinal analyses.**
Subjects: **Forty persons with recent spinal cord injury and 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 was measured with a spirometer. Maximum inspiratory and expiratory pressures (MIP and MEP), expressed in cmH_2O, were measured at the mouth.**
Results: **Both MIP and MEP were significantly positively associated with peak cough flow. After correction for confounders and time 10 cmH_2O higher MIP was associated with a 0.32 l/s higher peak cough flow, and a 10 cmH_2O higher MEP was associated with a 0.15 l/s higher peak cough flow. The association between MIP and peak cough flow was mainly based on within-subject variance. The association between MIP and peak cough flow was stronger than between MEP and peak cough flow.**
Conclusion: **Improvement in respiratory muscle strength is associated with improvement in cough capacity in persons with recent spinal cord injury who have impaired pulmonary function.**

Key words: spinal cord injury; respiratory muscles; expiratory airflow; cough; longitudinal analysis.

J Rehabil Med 2015; 47: 722–726

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Accepted Apr 24, 2015; Epub ahead of print Jun 12, 2015

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) (1–5). In this population a weak cough plays an important role in the development of serious respiratory complications such as atelectasis and pneumonia (6, 7). Cough is an important defence mechanism that serves to clear the airways from foreign material (in aspiration) and secretions (during infections) (8). In order to decrease the risk of respiratory complications, improvement of cough is an important goal in SCI-rehabilitation (9). Even though coughing is mainly characterized by forced expiratory activity, sufficient pre-cough inspiration is needed for it to be effective (8). 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 have shown that both inspiratory and expiratory muscle strength are associated with cough (10, 11). 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 they 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 in the design of intervention programmes that aim at improving cough effectiveness and help decrease the risk of respiratory complications. Therefore, the objective of the present analysis was to assess the longitudinal relationship between respiratory muscle strength and cough capacity in persons with recent SCI.

METHODS

Participants

For the present analysis we used data from a recently conducted randomized controlled trial (RCT) in which the effects of an added

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Journal Compilation © 2015 Foundation of Rehabilitation Information. ISSN 1650-1977

intervention (resisted inspiratory muscle training: RIMT) was compared with usual care (12). This trial was carried out at 4 rehabilitation centres 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 18–70 years, and impaired pulmonary function. Impaired pulmonary function was defined as forced expiratory volume in 1 s (FEV1) 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 RCT was approved by the Medical Ethics Committee of the Erasmus University Medical Centre in Rotterdam, the Netherlands. All participants gave informed consent.

Procedures

Measurements were performed 4 times. The first measurement (T0) was performed 4 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 tracheostomy. The follow-up measurements were performed approximately 9 weeks after T0 (T1), 17 weeks after T0 (T2), and 1 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. The intervention and allocation method have been described previously (12).

Measurements

Cough capacity. Cough capacity was measured with a spirometer (Oxycon Delta: CareFusion, Hoechberg, Germany). Persons were asked to cough as forcefully as possible after full inspiration through the mouth-piece (13). This manoeuvre was repeated 8 times; sufficient rest was given in between manoeuvres to prevent fatigue. 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 expiratory pressure measured at the mouth (MIP and MEP, respectively, expressed in cmH_2O) with the MicroRPM (CareFusion, Basingstoke, UK) using a flanged mouthpiece (14); MIP was measured after full expiration and MEP after full inspiration. Maximum pressure had to be maintained for at least 1 s. The highest value of 8 manoeuvres, 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 characteristics. Personal characteristics included age at the first test occasion, gender, smoking history (pack years before onset of SCI: number of cigarettes smoked per day × number of years smoked)/20), body mass index (BMI: body mass divided by height squared), prevalence of premorbid lung diseases, such as asthma or chronic obstructive pulmonary disease, and mobility (passive: with assistance or motorized wheelchair, or active: by manual wheelchair or walking). Lesion characteristics included lesion level and completeness (AIS score) (15), cause of SCI (traumatic or non-traumatic), and prevalence of trauma of the chest or lungs at onset of SCI (such as rib fractures, pneumothorax, and lung contusion).

Statistical analysis

To study the longitudinal association between respiratory muscle strength and cough, generalized estimating equation analyses (GEE) with an exchangeable correlation structure were used (16). 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. We checked whether the design of the primary study (allocation of persons to 1 of 2 groups: RIMT-group or control-group) influenced the longitudinal associations found, by adding "group allocation" as a covariate to the base models. Because the regression coefficient (beta) of the independent variable (MIP or MEP) did not change more than 10% we concluded that group allocation had no effect on the association found and that it was legitimate to combine the data of both groups.

The potential confounding effect of personal characteristics, lesion characteristics, respiratory history, and activity level on the association between respiratory muscle strength and cough was studied by adding these variables one at a time to the base model. 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: 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, BMI and mobility (passive or active) were entered as time-dependent variables (outcomes at each test occasion). Subsequently, a multivariate model was made with time, the independent variable (MIP or MEP) and all variables that showed a confounding effect. Finally, to detect whether the regression coefficient of the models described above, reflected mainly between-subject variance (cross-sectional association) or within-subject variance (longitudinal association), 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 associations, 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 analysed using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 20.0. Statistical significance was set at 0.05.

RESULTS

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

Table I. *Personal and lesion characteristics*

Characteristics	
Age, years, mean (SD)	46.8 (14.3)
Gender, men, *n* (%)	35 (87.5)
Smoking history, pack years, median [IQR]	11.3 [0.0–20.0]
Severity of lesion categories (21), *n* (%)	
C1–C4, AIS A, B, C	13 (32.5)
C5–C8, AIS A, B, C	10 (25.0)
T1–S5, AIS A, B, C	9 (22.5)
All AIS D	8 (20.0)
Tetraplegia, *n* (%)	30 (75.0)
Motor complete (AIS A and B), *n* (%)	24 (60.0)
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)

SCI: spinal cord injury; RIMT: resistive inspiratory muscle training; SD: standard deviation; IQR: interquartile range; AIS: American Spinal Injury Association Impairment Scale.

Table II. *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, l/s, mean (SD)	5.1 (1.8))	5.8 (2.0)	5.8 (1.9)	6.6 (1.9)
MIP, cmH_2O, mean (SD)	56.2 (26.2)	76.4 (29.2)	77.7 (26.7)	93.7 (32.7)
MEP, cmH_2O, mean (SD)	46.7 (26.4)	57.8 (26.8)	59.1 (28.6)	67.4 (32.2)
BMI, 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)

Passive mobility: with assistance or motorized wheelchair; BMI: body mass index; PCF: peak cough flow; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure.

The basic models showed a significant association between MIP and PCF (beta = 0.029, p = 0.006) and between MEP and PCF (beta = 0.017, p = 0.001). After correction for confounders these associations remained significant (Table III). 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 and time, a 10 cmH_2O higher MIP was associated with a 0.32 l/s higher PCF, and a 10 cmH_2O higher MEP was associated with a 0.15 l/s higher PCF.

After correction for confounders, the change model (Table IV) showed a significant association between change in MIP and change in PCF; an improvement of 10 cmH_2O in MIP was associated with an improvement of 0.27 l/s 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.

DISCUSSION

The results of the present analysis 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 associations. Therefore, we can conclude that associations were mainly based on within-

Table III. *Longitudinal association between respiratory muscle strength (MIP and MEP) and peak cough flow: GEE models with dependent variables and confounders*

	Model with MIP as independent variable			Model with MEP as independent variable		
Variables	Beta	SE	p	Beta	SE	p
Constant	3.284	0.497	0.000	2.848	1.263	0.024
T0–T1	0.125	0.197	0.523	0.541	0.181	0.003
T0–T2	0.168	0.205	0.412	0.567	0.204	0.005
T0–T3	0.122	0.245	0.618	0.818	0.240	0.001
MIP	0.032	0.006	0.000*	NE	NE	
MEP	NE	NE		0.015	0.005	0.006*
Confounders						
Smoking history, pack years	–0.007	0.010	0.480	–	–	
Body mass index	–	–		0.065	0.055	0.235

Outcomes are results of multivariable generalized estimating equation 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: 1 year after discharge inpatient rehabilitation; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; NE: not entered; *significant with $p < 0.05$; GEE: generalized estimating equation analyses.

Table IV. *Longitudinal association between change in respiratory muscle strength (ΔMIP and ΔMEP) and the change in peak cough flow: change model*

	Model with ΔMIP as independent variable			Model with ΔMEP as independent variable		
Variables	Beta	SE	p	Beta	SE	p
Constant	0.173	0.116	0.134	1.319	0.672	0.050
ΔMIP	0.027	0.008	0.001*	NE	NE	
ΔMEP	NE	NE		0.012	0.007	0.085
Confounders						
Smoking history, pack years	–0.006	0.003	0.023	–	–	
Body mass index	–	–		–0.036	0.022	0.095
Age	–	–		–0.003	0.005	0.591

Outcomes are results of multivariable generalized estimating equation 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: 1 year after discharge inpatient rehabilitation; ΔMIP: change in MIP, ΔMEP: change in MEP; NE; not entered; *significant with $p < 0.05$.

subject variance. This finding suggests that improvement of respiratory muscle strength may lead to an increase in cough capacity. To the best of our knowledge, longitudinal associations between respiratory muscle strength and cough capacity in persons with SCI have not been studied before.

In agreement with findings in previous cross-sectional studies on PCF, our results showed a stronger association with MIP than with MEP (10, 11). 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 (17). Pre-cough inspiration to high lung volumes optimizes expiratory pressures and enhances expiratory airflow during the expulsion phase of cough (8). 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 (8). 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 analysis showed that RIMT led to improvement in inspiratory muscle strength but not in cough capacity (12). 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 aforementioned RCT showed a mean additional effect of RIMT on MIP of 12 cmH_2O (12). In accordance with the associations found in the change model (Table IV) of the present analysis an increase this size may be associated with an increase in PCF with 0.32 l/s (12×0.027 (the beta of change in MIP), confidence interval: 0.13–0.52 l/s) when smoking history remains the same. This may not seem to be a large increase, but cough is seriously affected in many persons with SCI. Especially in the early phase after injury many persons with SCI are not able to produce an effective cough and are susceptible to accumulation of mucus (8, 18). Therefore, we feel that 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 (19), and therefore interventions to reduce the risk of respiratory complications should focus on this vulnerable group. In addition, the measurements were conducted in the first 18 months after injury. As lung tissue and ribcage are known to become progressively less compliant over the years, the association between respiratory muscle function and cough may be different in persons with chronic SCI (20).

This analysis has some methodological limitations. Unfortunately, there were missing data, in particular at the last measurement occasion. This may have weakened the associations that were found. Nevertheless, the use of sophisticated analysing methods enabled us to cope with the missing data and to use all available data. As a result, the sample size remained as large as possible and selection bias due to removing incomplete datasets was avoided. In addition, the method of measuring cough capacity may have influenced the results. Firstly, PCF was determined during a voluntary manoeuvre, which may differ from a spontaneous reflex-based cough (21). Secondly, maintaining a good seal around the mouth-piece may complicate the test. However, all participants were able to repeat this, somewhat unnatural, manoeuvre several times and maintained a good mouth seal around the mouth-piece. And finally, participants were tested in the seated position. The influence of the test position on the respiratory function measures may change due to changes over time in spasticity, seating position, and possibly other unknown factors.

In conclusion, the results of the present analysis showed that improvement of respiratory muscle strength is associated with improvement in cough capacity in persons with recent SCI who have impaired pulmonary function. Further research is necessary to gain insight into the causality of these associations and to study these associations in chronic SCI.

ACKNOWLEDGEMENTS

The authors would like to thank all participants and the participating rehabilitation centres and their research assistants and physicians who collected data from: Rijndam Rehabilitation Center (Rotterdam), Rehabilitation Center De Hoogstraat (Utrecht), Reade (Amsterdam), Heliomare (Wijk aan Zee).

This study was supported by the Kinderrevalidatie Fonds Adriaanstichting (grant no. 2007/0179-063).

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