

# Pulmonary Function of Patients with Chronic Neck Pain: A Spirometry Study

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**BACKGROUND:** Chronic neck pain is one of the most common musculoskeletal pain conditions experienced by many people during their lives. Although patients with neck pain are managed predominantly as musculoskeletal patients, there are indications that they also have poor pulmonary function. The aim of this study was to examine whether patients with chronic neck pain have spirometric abnormalities and whether neck pain problems and psychological states are associated with these abnormalities. **METHODS:** Forty-five participants with chronic neck pain and 45 well-matched healthy controls were recruited. Spirometry was used to assess participants' pulmonary function. Neck muscle strength, endurance of deep neck flexors, cervical range of motion, forward head posture, psychological states, disability, and pain intensity were also evaluated. **RESULTS:** The results showed that patients with chronic neck pain yielded significantly reduced vital capacity, FVC, expiratory reserve volume, and maximum voluntary ventilation ( $P < .05$ ), but peak expiratory flow, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC ratio were not affected ( $P > .05$ ). Strength of neck muscles, pain intensity, and kinesiophobia were found to be significantly correlated ( $r > 0.3$ ,  $P < .05$ ) with respiratory function. **CONCLUSIONS:** Patients with chronic neck pain do not have optimal pulmonary function. Cervical spine muscle dysfunction is parallel with pain intensity and kinesiophobia are factors that are associated mainly with this respiratory dysfunction. *Key words:* cervical pain; flows; maximum voluntary ventilation; respiration; spirometry; volumes. [Respir Care 2014;59(4):543–549. © 2014 Daedalus Enterprises]

## Introduction

Spirometry is a common test of pulmonary function that provides information regarding the presence of obstruction or possible restriction in people with suspected pulmonary dysfunction.<sup>1</sup> Pulmonary restriction is a term used to describe a group of respiratory disorders related to an im-

paired filling of the lungs with air.<sup>2</sup> Although a reduction in lung volume is a sign that is characteristic of restrictive disorders, respiratory flows and maximum voluntary ventilation (MVV) may also be affected.<sup>2-4</sup> This is particularly apparent in cases of neuromuscular weakness, as the respiratory muscles have a reduced ability to generate optimal levels of pressure and flow.<sup>3</sup> Neuromuscular weakness is also a physical sign in musculoskeletal pain conditions. However, musculoskeletal pain and pulmonary function are rarely considered together in clinical practice.

Chronic neck pain is a musculoskeletal condition affecting many people. Although patients with neck pain are managed predominantly as musculoskeletal patients, weakness and fatigue of cervical muscles, reduced cervical mobility, impaired proprioception, postural abnormalities, and psychological compromise have been argued to be factors that are associated with poor pulmonary function.<sup>5,6</sup> Despite mechanistic evidence suggesting that pulmonary function may be affected in those experiencing neck pain,<sup>5</sup> little is known of the actual respiratory function in this

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group. A previous pilot study has revealed trends toward pulmonary restriction in patients with chronic neck pain, but the small sample size did not allow confirmation of this restrictive pattern.<sup>6</sup> Furthermore, the association of well-known musculoskeletal and psychological manifestations of neck pain with function of the respiratory system remains completely unexplored.

Considering these gaps in the literature, this study was conducted to investigate pulmonary function in patients with chronic neck pain and to obtain data on the association between musculoskeletal and psychological manifestations of their pain with spirometric values.

## Methods

### Study Subjects

A convenience sample of 45 patients with chronic neck pain (> 6-mo duration, pain complaints at least once a week) was recruited and has been initially described in a previous publication.<sup>7</sup> Screening for eligibility was performed by using a health questionnaire. Patients were ineligible to participate if they were current or past smokers; had neck pain of traumatic origin; had pain in any other nonrelated body area; were obese (body mass index > 40), had clinical abnormalities or surgeries of the thoracic cage or vertebral column; had occupational industrial exposures; or had serious comorbidities (cardiorespiratory, neurological, musculoskeletal, neuromuscular, or/and psychiatric disorders), diabetes mellitus, or/and malignancies. Forty-five healthy controls<sup>7</sup> were additionally recruited by applying the same exclusion criteria and were individually matched with neck pain patients (same gender,  $\pm 5$  y of age,  $\pm 10$  cm in height, and  $\pm 10\%$  in weight). All assessments were undertaken at the Cardiorespiratory Laboratory of the Technological Educational Institute of Lamia in Central Greece during the period 2009–2010 after obtaining written informed consent. The study was approved by the Ethics Committee of the Department of Physiotherapy, School of Health and Caring Professions, Technological Educational Institute of Lamia, and the University of Manchester Ethics Committee.

### Study Design

The study was designed to compare the pulmonary function of patients with chronic neck pain with that of healthy controls and to examine correlations between spirometric indices with musculoskeletal and psychological parameters. Pulmonary function was examined using three different spirometric tests (vital capacity [VC], FVC, and MVV). Cervical function was assessed using neck isometric dynamometry (neck muscle strength), ultrasound-based motion analysis (cervical range of motion), lateral photographs

## QUICK LOOK

### Current knowledge

Chronic neck pain is one of the most common musculoskeletal pain conditions. Although patients with neck pain are managed predominantly as musculoskeletal patients, there are indications that poor pulmonary function is a common comorbidity.

### What this paper contributes to our knowledge

Patients with chronic neck pain have reduced vital capacity, expiratory reserve volume, FVC, and minute volume compared with predictive equations. Cervical spine muscle dysfunction in parallel with pain intensity and kinesiophobia are associated with respiratory dysfunction.

(forward head posture), and the craniocervical flexion test (endurance of deep neck flexors). Psychological states (anxiety, depression, catastrophizing, kinesiophobia) and pain characteristics were assessed through questionnaires. The assessment of cervical function and psychological states has been described in a previous publication.<sup>7</sup> All measurements were performed by an appropriately trained physiotherapist. A sample size calculation revealed that, for a large effect size ( $d = 0.8$ ), 26 participants were needed per group for a power of 80% (two-tailed hypothesis,  $P = .05$ ). However, 45 participants per group were recruited to increase statistical power and to account for potential missing data.

### Procedures

Spirometry was performed by using an electronic spirometer (Spirolab II, SDI Diagnostics, Easton, Massachusetts) and its accompanying software (WinspiroPRO, Medical International Research, Rome, Italy). Spirometry included three different pulmonary tests (VC, FVC, and MVV), which were performed according to the spirometer manual guidelines with special reference to the recommendations by the American Thoracic Society and European Respiratory Society.<sup>8,9</sup> VC and FVC maneuvers were performed from a standing position, whereas MVV maneuvers were performed from a sitting position. Participants used a nose clip in all tests to avoid any potential air leakage. They were asked to seal their mouths around the cylindrical carton mouthpiece and were verbally encouraged to ensure maximal performance throughout the tests. VC, FEV<sub>1</sub>, FVC, and peak expiratory flow (PEF) were reported from the maximum of the trials, and FEV<sub>1</sub>/FVC was calculated accordingly, whereas the average over the

trials was used for tidal volume, inspiratory capacity, and expiratory reserve volume. Forced expiratory flow at 25% (FEF<sub>25%</sub>), at 50% (FEF<sub>50%</sub>), at 75% (FEF<sub>75%</sub>), and from 25% to 75% (FEF<sub>25-75%</sub>) of forced expiration were also reported from the values of the best loop, which was defined as the one with the highest sum of FEV<sub>1</sub> and FVC.

Psychological parameters were measured through completion (in randomized order) of the cross-culturally validated Hospital Anxiety and Depression Scale,<sup>10</sup> Tampa Scale for Kinesiophobia,<sup>11</sup> and Pain Catastrophizing Scale.<sup>12</sup> Usual and current neck pain intensity, pain-induced disability, and physical activity level were assessed by administration of visual analog scales,<sup>13</sup> the Neck Disability Index,<sup>14</sup> and the Baecke Questionnaire of Habitual Physical Activity,<sup>15</sup> respectively.

Cervical range of motion assessment was actively performed in a standing position using an ultrasound-based motion analysis system (Zebris Medical GmbH, Isny, Germany) based on instructions provided in a previous publication.<sup>16</sup> Testing was performed with the participant's head in a neutral position while slowly performing three repetitions of each cervical movement. The best of the three repeats was recorded as the participant's range of motion in each direction. The procedure has been reported previously as very reliable (intraclass correlation coefficient [ICC] of 0.73–0.86, standard error of measurement of 6.5–8.5°).<sup>16</sup>

For assessing the forward head posture (FHP), participants were asked to stand as usual and to focus their vision on a predetermined reference point at a height level with their eyes. Three lateral photographs were then taken (HDR-SR11E digital color camera, Sony, Brussels, Belgium), and FHP was calculated from the mean of the three craniocervical angles (CVA) using 3-dimensional drawing software (Auto-CAD 2000, Autodesk, San Raphael, California). CVA was taken as the angle between the line extending from the tragus of the ear to the seventh cervical vertebra (C7) spinous process and the horizontal line through C7. This procedure is considered to be highly reliable (ICC 0.88).<sup>17</sup>

Neck flexor and extensor muscle strength was assessed in randomized order from a stabilized standing position with the head in a neutral position. The measurements were performed after a warm-up period with a custom-made isometric dynamometer with previously reported high reliability (ICC 0.9–0.96, standard error of measurement of 12.6–20.8 N).<sup>18</sup> Each participant performed three or more 5-s maximal isometric contractions until the two best measurements were within 10% of each other. The maximally recorded value was kept for the analysis.

Deep neck flexor endurance was examined using the craniocervical test, which has been previously reported by Jull et al.<sup>19</sup> A pressure biofeedback device (Stabilizer, Chattanooga Medical Supply, Chattanooga, Tennessee) was

placed under the cervical area of participants positioned in crook lying. Participants were required to perform a head-nodding action at 5 different pressure levels in increments of 2 mm Hg (from 22 to 30 mm Hg). A surrogate for endurance was taken as the maximal pressure that the participant could hold steady for 3 periods of 10-s without adopting any compensatory strategy. The test has been found to have satisfactory reliability (ICC 0.81–0.91).<sup>20,21</sup>

## Analysis

Patients with missing data and their matched controls were excluded from the analysis of the relative variable. Data were missing for left rotation and left lateral flexion range of motion (one patient with software problems), endurance of deep neck flexors (one patient without glasses), FHP (one control with a broken hairclip), and MVV (one control who refused to continue because of dizziness during the first trial). Means  $\pm$  SD were selected as measures of central tendency and dispersion. Differences between percent predicted pulmonary function parameters were examined using independent *t* tests and correlations with Pearson correlation coefficients. The software was set to calculate percent predicted values based on the combination of “E.R.S. '93/Knudson” norms.<sup>22,23</sup> Backward stepwise multiple regression analysis (removal = 0.1) was performed in patients with chronic neck pain for VC, PEF, and MVV by using the strength of neck extensors, endurance of deep neck flexors, sagittal range of motion, CVA, usual pain intensity, anxiety, depression, kinesiophobia, and catastrophizing as predictors. Analysis had a significance level equal to 0.05. The analysis of all data was performed with statistical software (SPSS 17, SPSS, Chicago, Illinois).

## Results

### Demographics and Pain Characteristics

The pain intensity of patients with chronic neck pain was mild to moderate (visual analog scale of 45.5  $\pm$  18.8 mm) but mild during the measurements (visual analog scale of 19.3  $\pm$  19.1 mm). The patients had mild disability (Neck Disability Index of 10.6  $\pm$  5.2) and pain chronicity of 69.6  $\pm$  57.6 mo. The demographics presented no significant difference between the two groups (Table 1).<sup>7,24</sup>

### Group Differences

The sample of patients used in this study was found to have reduced neck extensor strength, reduced active cervical mobility, and impaired function of the deep neck flexors compared with the control group (*P* < .05). A

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Table 1. Demographics of Patients With Chronic Neck Pain and Healthy Controls

	F/M	Age (Mean ± SD y)	Height (Mean ± SD cm)	Weight (Mean ± SD kg)	BMI (Mean ± SD kg/m <sup>2</sup> )	BQHPA (Mean ± SD)
Neck pain group	32/13	35.9 ± 4.5	165.8 ± 9.2	71.6 ± 16	25.9 ± 4.5	7.9 ± 1.3
Control group	32/13	35.4 ± 14	167.1 ± 8.7	72.3 ± 15.2	25.8 ± 4.4	7.6 ± 1.4

References 7 and 24

F/M = females/males

BMI = body mass index

BQHPA = Baecke Questionnaire of Habitual Physical Activity

Table 2. Differences in Spirometric Function (Percent Predicted) Between Patients With Chronic Neck Pain and Healthy Controls

% Predicted Values	Neck Pain (Mean ± SD)	Controls (Mean ± SD)	Mean Difference (95% CI)	r
VC	96 ± 14.8	103.4 ± 15	-7.4 (-13.6 to -1.1)*	0.24
IC	96.9 ± 19.9	101.2 ± 21	-4.2 (-12.8 to 4.3)	0.10
ERV	85.7 ± 30.8	98.2 ± 28.8	-12.6 (-25.1 to -0.0)*	0.21
FEV <sub>1</sub>	103.1 ± 13.8	106.6 ± 15.7	-3.5 (-9.7 to 2.7)	0.12
FVC	103.4 ± 11.8	110 ± 16.7	-6.5 (-12.6 to -0.5)*	0.22
FEV <sub>1</sub> /FVC	103.5 ± 6.1	101.5 ± 6.8	2.1 (-0.6 to 4.8)	0.16
FEF <sub>25%-75%</sub>	92.4 ± 20.8	92 ± 23.3	0.4 (-8.8 to 9.6)	0.01
FEF <sub>25%</sub>	94.4 ± 18.5	100.6 ± 20.6	-6.2 (-14.4 to 2)	0.16
FEF <sub>50%</sub>	91.1 ± 21.8	90.2 ± 25.3	0.9 (-9 to 10.8)	0.02
FEF <sub>75%</sub>	80.4 ± 26	79.1 ± 26.6	1.3 (-9.7 to 12.3)	0.03
PEF	98.1 ± 15.8	102.7 ± 17.9	-4.6 (-11.6 to 2.5)	0.14
MVV	92.2 ± 20.7	104.4 ± 21.7	-12.2 (-21.2 to -3.2)†	0.28

\*  $P < .05$

†  $P < .01$

VC = vital capacity

IC = inspiratory capacity

ERV = expiratory reserve volume

FEF<sub>25-75%</sub> = forced expiratory flow from 25% to 75% of forced expiration

FEF<sub>25%</sub> = forced expiratory flow at the 25% of forced expiration

FEF<sub>50%</sub> = forced expiratory flow at the 50% of forced expiration

FEF<sub>75%</sub> = forced expiratory flow at the 75% of forced expiration

PEF = peak expiratory flow

MVV = maximum voluntary ventilation

trend toward reduced neck flexor strength was also observed. Head posture, anxiety, and depression were similar to healthy controls ( $P > .05$ ).<sup>7,24</sup>

Patients with chronic neck pain had significantly decreased VC, expiratory reserve volume, FVC, and MVV ( $P < .05$ ). All other spirometric indices were not significantly different ( $P > .05$ ) (Table 2). Two patients with chronic neck pain were found to have mild restriction (percent predicted FVC < lower limit of normal but  $\geq 70$ , no reduction in FEV<sub>1</sub>/FVC),<sup>25</sup> whereas the others were found to have normal lung function.

**Correlations**

VC was significantly correlated with neck muscle strength ( $r = 0.67-0.68$ ), usual pain intensity ( $r = -0.32$ ), and kinesiophobia ( $r = -0.39$ ,  $P < .05$ ), whereas a trend

was observed for its correlation with catastrophizing ( $r = -0.26$ ). MVV was significantly correlated with neck muscle strength ( $r = 0.57-0.63$ ), usual pain intensity ( $r = -0.32$ ), and kinesiophobia ( $r = -0.35$ ,  $P < .05$ ). PEF was significantly correlated with neck muscle strength ( $r = 0.64-0.72$ ) and usual pain intensity ( $r = -0.39$ ,  $P < .05$ ), whereas a borderline trend was observed for its correlation with kinesiophobia ( $r = -0.29$ ) (Table 3).

**Regression Analysis**

In the prediction models of VC, MVV, and PEF, a significant fit to the data overall was observed ( $P < .05$ ), with only neck extensor strength remaining a significant predictor (Table 4). Multiple correlation coefficients and generalizability of the prediction models of VC ( $R = 0.7$ ,  $R^2 = 0.49$ , adjusted  $R^2 = 0.47$ ), MVV ( $R = 0.65$ ,  $R^2 = 0.43$ ,

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Table 3. Correlations Between Chronic Neck Pain Manifestations and VC, MVV, and PEF

	r		
	VC	MVV	PEF
Strength of neck extensors	0.68*	0.63*	0.72*
Strength of neck flexors	0.67*	0.57*	0.64*
Endurance of deep neck flexors	0.11	0.22	0.25
ROM in sagittal plane	0.01	0.02	-0.16
ROM in frontal plane	0.15	0.06	-0.05
ROM in transverse plane	0.18	0.13	0
Craniocervical angle	0.09	0.02	0.05
Usual pain intensity	-0.32†	-0.32†	-0.39**
Current pain intensity	-0.03	-0.1	-0.04
Neck Disability Index	-0.12	-0.2	-0.22
Anxiety	-0.22	-0.22	-0.25
Depression	-0.01	-0.03	-0.1
Kinesiophobia	-0.39**	-0.35†	-0.29
Catastrophizing	-0.26	-0.13	-0.23

\*  $P < .001$

†  $P < .05$

\*\*  $P < .01$

VC = vital capacity

MVV = maximum voluntary ventilation

PEF = peak expiratory flow

ROM = range of motion

Table 4. Regression Models for the Prediction of VC, MVV, and PEF

	B (95% CI)	SE B	$\beta$
VC prediction			
Constant	2.34 (1.87–2.8)*	0.23	
Strength of neck extensors	0.08 (0.06–0.11)*	0.01	0.7
MVV prediction			
Constant	67.26 (49.81–84.72)*	8.65	
Strength of neck extensors	2.71 (1.73–3.69)*	0.49	0.65
PEF prediction			
Constant	4.74 (3.86–5.63)*	0.44	
Strength of neck extensors	0.17 (0.12–0.22)*	0.03	0.72

Beta values (B) with their 95% CI and standard error (SE B) as well as the standardized beta values ( $\beta$ ) for the prediction of vital capacity (VC), maximum voluntary ventilation (MVV), and peak expiratory flow (PEF) in patients with chronic neck pain

\*  $P < .001$

adjusted  $R^2 = 0.41$ ), and PEF ( $R = 0.72$ ,  $R^2 = 0.52$ , adjusted  $R^2 = 0.51$ ) were satisfactory. The assumption of independent errors, homoscedasticity, linearity, and normally distributed errors was met, and no influential outlier was detected.

Discussion

Patients with chronic neck pain have been found to have reduced respiratory strength<sup>7</sup> and changes in their blood

chemistry.<sup>24</sup> The results of the present study show that patients with chronic neck pain have additionally decreased lung volumes and MVV, and this seems to be related to neck flexor and extensor strength, pain intensity, and kinesiophobia.

In agreement with a previous study,<sup>6</sup> time-point flows, PEF, and FEV<sub>1</sub>/FVC ratio were not found to be affected, but FVC and VC were found to be reduced in patients with chronic neck pain.

Reduction in lung volumes is usual in both obstructive<sup>26</sup> and restrictive<sup>2,3</sup> pulmonary disorders, and reduced FEV<sub>1</sub>/FVC ratio is a sensitive index of pulmonary disorders particularly when a pulmonary obstruction is present.<sup>26-28</sup> In contrast, in restrictive disorders, this index can be presented as increased or normal.<sup>27,28</sup> The normal FEV<sub>1</sub>/FVC ratio in chronic neck pain patients indicates therefore that reductions in lung volumes are more likely to be associated with pulmonary restriction than obstruction. This belief is further supported by the fact that VC was not higher than FVC, in contrast to what would be expected in obstructions.<sup>1</sup>

Patients with chronic neck pain also presented normal peak and time-point respiratory flows. Reduced peak respiratory flows can be observed in both restrictive and obstructive disorders.<sup>1,3,26</sup> However, the present study does not provide enough evidence to support a change in peak flows. Furthermore, the fact that the time-point flows (FEF<sub>25%</sub>, FEF<sub>50%</sub>, FEF<sub>75%</sub>, and FEF<sub>25-75%</sub>) were not affected further supports the assertion that an obstruction was not apparent.

In agreement with previous pilot study findings,<sup>6</sup> the present study also showed that patients with chronic neck pain demonstrated a decline in MVV. MVV is a general index of respiratory function depending on airway resistance, respiratory muscle function, lung and chest wall compliance, and ventilatory control mechanisms.<sup>29,30</sup> Furthermore, MVV is an index of maximal breathing capacity during dynamic exercise.<sup>1,30</sup> MVV is also associated with neuromuscular control, and its reduction in neck pain patients may imply further interference in the nervous system.<sup>6,8,9</sup> This index can be presented as reduced in both obstructive and restrictive disorders.<sup>4,9,31</sup> Thus, the reduction in MVV and the findings on lung volumes contribute to the notion that the respiratory decline observed in patients with chronic neck pain seems to follow a rather restrictive pattern.

According to the results of the present study, respiratory dysfunction in patients with chronic neck pain is associated mainly with cervical muscle dysfunction, pain intensity, and kinesiophobia. Weakness of common cervical muscles (sternocleidomastoid, scaleni, and trapezius) may have had a direct effect on respiratory function but could have led to muscle imbalances and spinal instability<sup>32,33</sup> through an effect on the rib cage mechanics and conse-



quentially the biomechanical function of the respiratory muscles.<sup>5,33</sup> These mechanical changes in respiratory muscles may influence their ability to generate appropriate force levels<sup>6</sup> and can lead to permanent respiratory weakness due to plastic changes.<sup>34</sup> This respiratory weakness can lead to dysfunction of the respiratory pump, compromising its ability to produce optimal maximal flows and to expand the lungs and consequently leading to a general deterioration of respiratory performance.<sup>3</sup>

Pain and kinesiophobia may also constitute inhibiting factors during respiratory maneuvers, impeding patients from exerting maximal effort. However, their role seems to be rather indirect. Kinesiophobia can lead to cervical movement avoidance during daily activities, whereas pain can also change the motor control patterns for limiting the use of painful muscles.<sup>35</sup> These changes may not be optimal for maximal force production and may become a permanent situation due to plastic muscle adaptations.<sup>34</sup> Thus, both pain and kinesiophobia may alter cervical biomechanics, further contributing to the development of respiratory dysfunction in chronic neck pain patients.

The overall findings of the present study show an important clinical trend in patients with chronic neck pain. Despite subjects' compromise not being sufficient to classify them as respiratory patients, the spirometric function of patients with chronic neck pain presents a pattern similar to pulmonary restrictive disorders and especially neuromuscular weakness. In the long term, the reduction in lung flow and volumes may render the lung tissues, spinal articulations, and rib cage stiffer, further contributing to the development of a restrictive pattern.<sup>36</sup> Furthermore, it may be expected that patients with more serious neck pain may experience greater effects on their respiratory systems, and in more severe cases, they might manifest respiratory pathology.

Independent of the development of a pathologic pulmonary restriction, patients with chronic neck pain present an obvious respiratory dysfunction that necessitates clinical consideration. Future studies should be performed in patients with a greater range of pain and disability. Furthermore, use of plethysmography or other pulmonary function tests can enhance scientific knowledge about the pulmonary function of these patients. The close neuro-anatomical relation of the cervical region to pulmonary function could also lead researchers to question whether patients with pulmonary diseases may also develop neck pain. Finally, the findings of this study reveal a need for case studies or randomized control trials to examine the effectiveness of therapies including respiratory rehabilitation techniques in patients with chronic neck pain.

The main limitation of this study is the potential existence of bias since the participants were not randomly recruited and blind assessors were not used. Moreover, the lack of examination of residual volume and consequen-

tially of total lung capacity did not permit us to present the full picture of lung volumes in patients with neck pain, especially considering that a low total lung capacity is an important index for defining a true pulmonary restriction. Furthermore, the examination procedure was quite long with potential testing effects. The incorporation of a number of tests was considered necessary to obtain a more complete picture of this respiratory dysfunction. However, the examination of spirometric changes before the assessment of cervical function parameters protected the validity of the pulmonary function indices.

## Conclusions

In conclusion, patients with chronic neck pain seem to have manifestations of respiratory dysfunction that are quite similar to those presented in respiratory patients with neuromuscular weakness. The origins of this weakness are believed to be related to the dysfunction of cervical muscles, whereas pain and kinesiophobia may further contribute directly or indirectly to the development of this dysfunction. The results of this study support the incorporation of respiratory assessment and rehabilitation into the usual treatment of patients with chronic neck pain. However, the effectiveness of such approaches requires further experimental investigation.

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