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Clin Rehabil 2005 19: 426
DOI: 10.1191/0269215505cr782oa

Clinical Rehabilitation 2005; **19:** 426–432

Effects of multiple sclerosis on respiratory functions

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Received 29th December 2003; returned for revisions 30th March 2004; revised manuscript accepted 8th June 2004.

Objectives: To measure respiratory functions of ambulatory patients with multiple sclerosis and compare the results with expected values from healthy general population data. Further, to study the correlation of respiratory function impairment with the multiple sclerosis-induced disability level.
Subjects: Thirty-eight patients with definite diagnosis of multiple sclerosis from the multiple sclerosis outpatient clinic.
Methods: The Expanded Disability Status Scale (EDSS) scores (mean 4.34 ± 1.39) were evaluated to measure disability level. Respiratory functions tested in the laboratory included spirometric (FVC, FEV_1, FEV_1/FVC), maximal inspiratory (MIP) and expiratory (MEP) mouth pressure measurements. Patients were clinically assessed using a pulmonary dysfunction index (PDI) and dyspnoea index; various breathing features were also recorded.
Results: With respect to expected values from healthy general population, important decreases were found in mouth pressures with MIP ($77\% \pm 23\%$, $p \cong 0$) and MEP ($60\% \pm 13\%$, $p \cong 0$) while spirometric measures were significantly but less affected (FVC $94\% \pm 12\%$, $p < 0.01$, FEV_1 $91\% \pm 16\%$, $p < 0.001$). FEV_1/FVC ratios were normal. Notable increases in PDI (5.58 ± 0.68, $p \cong 0$) and dyspnoea index (0.32 ± 0.47, $p \cong 0$) were observed. Significant relationships ($p < 0.01$) between respiratory function impairment and the multiple sclerosis disability level could be detected for FVC, MEP and PDI.
Conclusions: Multiple sclerosis clearly impairs respiratory functions; maximal mouth pressures are more severely reduced. This impairment increases with multiple sclerosis-induced disability level but is found to be independent from duration of disease.

Introduction

Multiple sclerosis is a disease characterized by demyelination of the central nervous system and shows varied symptoms depending on the localization, size and number of lesions. It is the most common cause of neurological disability in young adults.[1–3] Even though few pulmonary problems are observed in patients with multiple sclerosis, during the terminal stage morbidity and mortality are often caused by pulmonary complications such as aspiration pneumonia, atelectasis or acute respiratory deficiency.[4–6]

The three most common respiratory problems in multiple sclerosis are respiratory muscle weakness, bulbar function impairment and abnormalities of breathing control.[4,7] Recent studies have shown

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10.1191/0269215505cr782oa

expiratory muscle weakness is manifest in patients with multiple sclerosis.[8–11]

The principal objective of the present study is to compare the differences in the respiratory functions between patients with multiple sclerosis and the expected values from (healthy) general population with emphasis on the earlier stages of the disease. Further, the evolution of respiratory function loss with multiple sclerosis induced disability level is investigated.

Patients and methods

Patients

Thirty-eight patients (22 males and 16 females) with mean age 39.1 ± 7.1 years (range 22–50) meeting the criteria of Poser *et al.*[12] for the diagnosis of definite multiple sclerosis were recruited to the study from the multiple sclerosis outpatient clinic in the neurology department of Cerrahpasa Medical School, Istanbul University. Special attention was paid to exclude from the study patients whose medical status could interfere with the research objectives. Accordingly, patients with any diagnosed pulmonary diseases, including chronic obstructive pulmonary disease, tuberculosis and chronic bronchitis, were excluded from the study, as were all cases with bulbar dysfunction which is known to cause respiratory impairment[4]; the latter was ascertained by neurological examination and magnetic resonance imaging findings. Also, none of the patients was in a period of relapse; relapsing remitting type patients (12 cases) had had no attacks in the past three months, while secondary progressive (19 cases) and primary progressive (7 cases) type patients had had zero or at most half point increases in their Expanded Disability Status Scale (EDSS) scores in the last six months before the tests. Finally, all cases had EDSS scores ≤ 6.5 and none were bedridden or wheelchair bound; 18 patients were ambulatory without assistance, 20 required a cane or crutches for ambulation.

The selected patients were informed about the study; all agreed to participate and appointments for tests and assessments were co-ordinated with their private schedules.

Clinical assessments

Demographic and clinical parameters

The height and weight of the patients was measured and their body-mass index (BMI)[13] was computed. The standard Kurtzke EDSS, which was scored independently from our pulmonary measurements by a neurologist, was used to describe each subject's global level of function. The EDSS provides a score ranging from zero, indicating normal neurological findings, to 10, indicating death from MS.[14]

Smoking

It is known that smoking has a negative effect on respiratory functions and the severity of impairment depends on the number of packs smoked per day in the past. To evaluate the effects of smoking quantitatively, each patient was assigned a smoking index (currently smoking = 2, past smokers who quit during the last two years = 1, non smokers = 0). This index was used to compute the smoking intensity[15] defined as:

$$\begin{aligned} &\textit{Smoking intensity} \\ &\quad = (\textit{Smoking index}/2) \times \{(\textit{quantity}/\textit{day})/20\} \\ &\qquad \times \{\textit{years smoked})/10\} \end{aligned}$$

Respiratory parameters

Pulmonary function and mouth pressure tests measurements were performed at the cardiopulmonary laboratory in the Cardiology Institute of Istanbul University by a physiotherapist who was blinded to the EDSS scores. During spirometric and mouth pressure tests the patients were seated in upright position on a chair and a noseclip was positioned to prevent air leaks.

Spirometric tests[16]

Spirometric measurements (forced vital capacity-(FVC), forced expiratory volume in one second-(FEV_1) were obtained using a Vitalograph device. The best value obtained from at least three efforts, measured at 3 min intervals, was used. Measured parameters were converted into predicted value percentages using Kamburoff–Voitovits[17] nomogram. FEV_1/FVC ratios were computed from FEV_1 and FVC measurements.

Mouth pressure measurements

The tests were performed using SensorMEDICS brand Micro-MPM device. For both maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in all patients we performed several practice tests in order to correct possible training and learning effect. Measurements were repeated until three technically satisfactory and consistent values were obtained. The highest value was used in data analysis. Measured values were normalized to predicted value percentages as recommended by the instrument instruction manual.[18]

Breathing characteristics

With patients sitting in an upright position, breathing type (costal–C, diaphragmatic–D) and depth (normal–N, superficial–S) were noted and breathing frequency at rest was recorded. Since normal chest and diaphragm movement has a two-chest, two-diaphragm breathing pattern,[19] the following scale was used to classify the breathing type: 0C/4D–diaphragmatic only, 1C/3D–diaphragmatic dominated, 2C/2D–mixed, 3C/1D–costal dominated, 4C/0D–costal only. Patients were also questioned on their complaints about cough, sputum and dyspnoea symptoms.

Pulmonary Dysfunction Index (PDI)

The PDI, which was devised by Smeltzer[20] as a clinical predictor of respiratory dysfunction in MS patients, was used in the study. This index is comprised of clinical signs which include a weakened cough as rated by the examiner, the patient's ability to count on a single exhalation and patient's report of a weak cough and difficulty clearing pulmonary secretions. The summed PDI score is classified as low (scores of 4–5), medium (scores of 6–8) or high (scores of 9–11), with higher scores correlating with increasing respiratory difficulties.

Dyspnoea index

Four-scale dyspnoea index[21] was used following the recommendations of the American Thoracic Society (0–normal, 1–mild, 2–moderate, 3–severe, 4–very severe).

Statistical analysis

For parameters for which a widely accepted prediction formula exist, results were converted to percentages of healthy population predicted values. Quantitative methods made use of Smith–Satterthwaite corrected two-tailed Student's t-test or Mann–Whitney U-test depending on intra-group variance analysis F-test results. For non-parametric data analysis, χ^2 or Fisher tests were applied, as dictated by the data set characteristics. For correlation analysis Pearson's linear regression formulas were used.

Possible correlations were investigated between the smoking intensity and the spirometric test results of our patients. The test results obtained for each patient were converted to a second set of predicted values which depended on their smoking intensity.[15] The differences between the predicted values obtained with and without smoking intensity corrections for FVC and FEV_1 were subjected to a linear correlation analysis with respect to related smoking intensities.

Results

The demographic and multiple sclerosis characteristics of the patients studied are summarized in Table 1.

Four patients were underweight (BMI < 20 kg/m^2) and two could be considered obese (BMI $>$ 30 kg/m^2). Neurological examination has shown 36 patients with pyramidal signs (22 paraparesia, eight tetraparesia, four hemiparesia and paraparesia, two monoparesia) and two with cerebellar signs. The average functional disability level as assessed by EDSS scores obtained (4.34) corresponds to a mild to moderate disability with the

Table 1 Characteristics of the study sample ($n = 40$)

Characteristic	Mean (SD)	Range
Age (years)	39.1 (7.1)	22–50
Sex (male/female)	22M/16F	
BMI (kg/m^2)	24.5 (3.8)	16.5–31.7
Smoking (yes/quit/no)	18/2/18	(M:12/2/8, F:6/0/10)
Smoking intensity (decade × packs/day)	0.67 (0.90)	0.0–3.0
Multiple sclerosis duration (years)	9.2 (5.1)	2–20
EDSS	4.34 (1.39)	1.5–6.5

EDSS, Expanded Disability Status Scale; BMI, body mass index.

average patient fully ambulatory without aid (able to walk without aid or rest for some 500 m).

The correlation analysis of the predicted value variations taking into account the smoking intensity corrections pointed to almost total independence of FVC and FEV_1 variations with smoking intensity ($r^2 < 0.02$) and consequently the effects of smoking have not been further considered in our discussion.

The results for the pulmonary function tests, mouth pressure measurements and pulmonary indices are presented in Table 2, which also contains the statistical difference analysis results of these measurements with respect to expected values from healthy general population data. With respect to critical thresholds recommended by the American Thoracic Society,[15,16] five patients were classified as critical for FVC < 80%, 12 patients for FEV_1 < 80% and only two patients for FEV_1/FVC < 75%.

Breathing type was observed to be mostly costal dominated (3C/1D: 55%, 2C/2D: 37%, 1C/3D: 5%) with only one case truly (0C/4D) diaphragmatic. However, this type distribution was not significantly different from the 2C/2D type normal breathing pattern. None of our patients had any complaints about coughing and sputum.

Mild dyspnoea was reported by 12 patients, which is significantly different ($p \cong 0$) from the rate in the normal population. Breathing frequency was 19.3 (3.7) per min, which is in the higher end of the generally observed range of 10–20.[22]

The effect of functional disability level on the degree of respiratory impairment has been investigated by correlating all the test measurements with EDSS scores. Significant correlations ($p < 0.01$) were found for FVC ($r = -0.42$), MEP ($r = -0.39$) and PDI ($r = +0.45$). Figure 1 shows the partial averages of the obtained FVC, FEV_1, MEP and PDI data ordered by increasing EDSS score bands.

Possible interdependencies of spirometric results and PDI with mouth pressures were analysed by cross-correlating obtained test results. Table 3 summarizes the relationships found; FEV_1/FVC and dyspnoea index were not significantly correlated with mouth pressures.

Further analysis has shown that EDSS scores are weakly correlated with the disease duration ($r = +0.37$, $p < 0.02$). No correlations could be found between any of the test results obtained and multiple sclerosis duration (all $r^2 < 0.03$).

Table 2 Comparison of respiratory functions between patients with multiple sclerosis and healthy population

Parameter (unit)	Mean result[a]	% predicted[a]	*p*-value
FVC (L)	3.82 (1.02)	94 (12)	$p < 0.01$
FEV_1 (L)	3.03 (0.94)	91 (16)	$p < 0.001$
FEV_1/FVC	81% (10)	98 (12)	N.S.
MIP (cmH_2O)	67.47 (23.67)	77 (23)	$p \cong 0$
MEP (cmH_2O)	73.05 (23.82)	60 (13)	$p \cong 0$
Breathing depth (N/S)[b]	33/5		$p < 0.02$
PDI (4–11)[b]	5.58 (0.68)		$p \cong 0$
Dyspnoea index (0–4)[b]	0.32 (0.47)		$p \cong 0$

[a]Values given as mean (SD).
[b]Healthy general population expected values are: PDI = 4, dyspnoea index = 0 and breathing depth = N.
N, normal; S, superficial; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PDI, pulmonary dysfunction index.

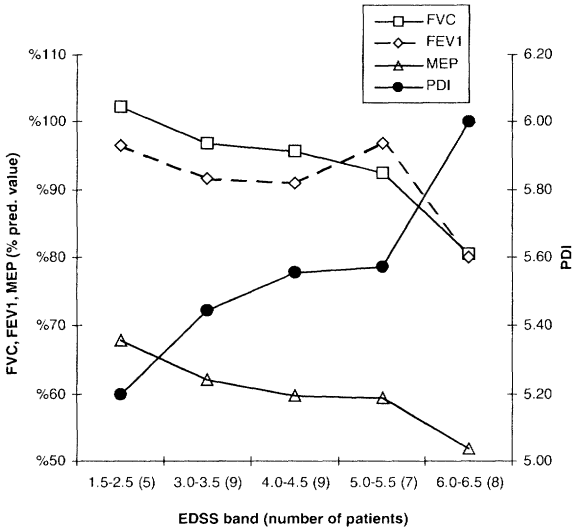

Figure 1 Pulmonary test results distribution per EDSS category of patients with multiple sclerosis.

Table 3 Significant correlations[a] of pulmonary tests versus mouth pressures of patients with multiple sclerosis

Parameter	MEP		MIP	
	r	*p*-value	*r*	*p*-value
FVC	+0.48	$p<0.005$	+0.41	$p<0.01$
FEV_1	+0.37	$p<0.05$	+0.24	N.S.
PDI	−0.43	$p<0.01$	−0.22	N.S.
MIP	+0.57	$p<0.001$	–	–

[a] Pearson's linear regression analysis was used.
FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PDI, pulmonary dysfunction index.

Discussion

This study investigates the presence and the progression of impairment in pulmonary function of patients with multiple sclerosis with relatively low degrees of disability. The results of a variety of noninvasive tests have been compared with values expected from a healthy normal population.

Mouth pressures

Although none of the patients participating had any respiratory deficiency complaints, test results definitely show significant ($p \cong 0$) and important reduction of mouth pressures. Observed average decrease of 23% in MIP as compared with 40% in MEP agree with earlier reports signalling more pronounced expiratory than inspiratory muscle weakness in with multiple sclerosis patients.[7,9,10,23] The results obtained are consistent with the findings of Smeltzer *et al.*[23] (40 patients, average. age 40) but higher then those of Buyse[10] (60 patients, avg. age 48) and Foglio[11] (24 patients, avg. age 48). The rather large discrepancy with the latter studies are probably due to different normalization equations used for calculating expected values and the age difference. We note, however, that all of the previous reports concerned patients with higher of functional disability with average EDSS scores reaching 7.0, 6.5 and 5.3 respectively.

Clinical messages

- Ambulatory patients with multiple sclerosis have impaired respiratory functions; mouth pressures are more severely affected.
- Pulmonary disability increases with severity of multiple sclerosis but is independent from MS duration.
- Pulmonary dysfunction index is effective for early detection of multiple sclerosis induced expiratory weakness.
- Early training to prevent respiratory complications during later stages of multiple sclerosis should be researched.

Pulmonary function tests

Spirometric pulmonary function tests have shown a somewhat less pronounced reduction (-6% for FVC, -9% for FEV_1) in respiratory volumes. Although close to normal expected values, these results were found to be very significantly reduced. Again, our results are consistent with those of Smeltzer *et al.*[23] but higher than those of Buyse *et al.*[10] The average FEV_1/FVC ratio, an indicator of airway obstruction, was found to be almost normal at 98% of the predicted value. Smeltzer *et al.*[23] and Buyse *et al.*[10] have also reported FEV_1/FVC ratios close to but significantly lower than normal levels.

Fourteen per cent of our patients were under the critical thresholds for FVC and 32% for FEV_1. However, due to parallel reduction of FEV_1 and FVC test results, only 5% were below the critical FEV_1/FVC level, which tends to confirm the infrequent early occurrence of obstructive lung disease in multiple sclerosis.[4,9,23] This is in opposition to findings in more functionally impaired patients (average EDSS 6.5) by Buyse *et al.*[10] who reported 31% obstructive dysfunction which was in part tied to effects of the smoking.

Correlation analysis with EDSS

We found weak but significant correlation of MEP, FVC and PDI with EDSS scores. These correlations were reported to be much stronger by Gosselink *et al.*[8] for MEP and MIP with respect to EDSS but for extremely impaired patients (average EDSS 8.5). Smeltzer *et al.*[23] employing a different statistical procedure (ANOVA for patient groups categorized by their ambulation level), observed significant reduction of MEP with ambulation impairment (which agrees with our observations)

but could also not correlate MIP with EDSS scores.

Correlations with disease duration

Our findings show a weak but significant ($p < 0.02$) correlation of EDSS scores with multiple sclerosis duration but point to almost total independence of respiratory impairment from disease duration. Buyse *et al.*,[10], like Klaveren *et al.*,[24] also found no relation between duration of multiple sclerosis and pulmonary test measurements but, in contrast to our results although confirming those of Foglio *et al.*,[11] they could not correlate most results with EDSS scores either. Our results tend to agree with those of Smeltzer *et al.*,[23] who studied a more disabled group (average EDSS 7). We believe that severity of multiple sclerosis rather than its duration is the principal cause of respiratory weakness as noted by Gosselink *et al.*,[5]

Cross-factor analysis

As expected, MEP and MIP were found to be interrelated. Analysis shows that while MEP results were significantly correlated with FVC, FEV_1 and PDI, only FVC data have shown conclusive dependency with MIP results. Both Gosselink *et al.*,[8] and Smeltzer *et al.*,[20] detected a similar relation between MEP and PDI, although for more severely affected patients. These results should be expected, since FEV_1 and PDI are primarily dependent on expiratory muscle strength (directly measured with MEP) while FVC also depends on air volume inspired initially which depends on inspiratory muscle strength (directly measured by MIP).

Pulmonary dysfunction index (PDI)

It is interesting to note that the PDI scores of our patients with multiple sclerosis patients were significantly higher than normal. PDI average (5.58) for our patients indicates a significant medium-level reduction of expiratory muscle strength. Gosselink *et al.*,[8] reported a higher average PDI (10.0) for considerably more affected patients (mean EDSS 8.5). Moreover, we found a significant correlation of PDI with MEP test results and EDSS scores. The PDI score evaluation is very rapid and practical, yet our results show it can correctly point to respiratory deficiency symptoms even for weakly affected patients and recommend the use of this index for early detection of expiratory muscle dysfunction in multiple sclerosis.

Dyspnoea

It is known that with multiple sclerosis patients rarely complain of dyspnoea even when severe disability and impaired respiratory muscle strength are apparent; this was previously related to restricted motor activities and greater expiratory than inspiratory muscle dysfunction.[7,25] None of our patients, all self-ambulatory, had any respiratory complaints during their normal daily activities, yet mild dyspnoea under moderate exertion was reported by 32% of them, a result that deviates significantly from that in the healthy population.

Breathing characteristics

Our results also indicate that patients with multiple sclerosis tend to have a more superficial and faster breathing pattern than healthy populations. A significantly higher breathing rate was also reported (20.5/min) in a study of 11 moderately disabled (EDSS 6.5) patients with multiple sclerosis by Tantucci *et al.*[26] The breathing type of our patients was not significantly different from normal even though our data indicate a trend towards a more costal dominated type of breathing.

In this study, due to difficulties with patients' access to laboratory premises, we could not repeat laboratory tests for each patient in two separate sessions to avoid the 'learning effect' as recommended.[27]

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