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ORIGINAL REPORT

COMPARISON OF FUNCTIONAL EXERCISE CAPACITY, PULMONARY FUNCTION AND RESPIRATORY MUSCLE STRENGTH IN PATIENTS WITH MULTIPLE SCLEROSIS WITH DIFFERENT DISABILITY LEVELS AND HEALTHY CONTROLS

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Objective: **To compare functional exercise capacity, pulmonary function and respiratory muscle strength in fully ambulatory patients with multiple sclerosis with different disability levels and healthy controls, and to elucidate the determinant factors of functional exercise capacity.**

Methods: **Forty-three fully ambulatory patients with multiple sclerosis and 30 healthy controls were included in the study. Patients were grouped according to Expanded Disability Status Scale (EDSS); Group I (EDSS 0–2), Group II (EDSS 2.5–4.5). Functional exercise capacity was evaluated using a six-minute walk test, and measurement of pulmonary function, and maximal inspiratory and expiratory pressures (MIP, MEP). The Pulmonary Index was used as a clinical predictor of respiratory dysfunction.**

Results: **Respiratory muscle strength was lower in multiple sclerosis groups compared with controls, but the difference in MIP and %MIP did not reach statistical significance in Group I. The six-minute walk test distance was significantly shorter and peak expiratory flow was lower in multiple sclerosis groups ($p < 0.05$). Of the variance in the six-minute walk test distance, 75% was explained by EDSS ($R^2 = 0.55$, $p < 0.001$), difference in heart rate ($R^2 = 0.06$, $p = 0.007$), age ($R^2 = 0.05$, $p = 0.009$) and gender ($R^2 = 0.09$, $p = 0.003$).**

Conclusion: **Respiratory muscles are weakened, functional exercise capacity is reduced and pulmonary function is affected even in the early phase of multiple sclerosis. Ambulatory patients with multiple sclerosis who have a higher level of disability have lower pulmonary function, respiratory muscle strength and functional capacity than less disabled ones and controls. Neurological disability level, age, gender and heart rate difference on exertion are the determinants of functional exercise capacity.**

Key words: multiple sclerosis; respiratory muscles; pulmonary function; exercise test.

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (1). Respiratory problems are common in the terminal stage of MS, and nearly half of patients die from pulmonary complications, such as aspiration pneumonia (2–4).

Respiratory muscle weakness is usually described in the advanced phase of MS (5–8), and little research has been published on the evaluation of respiratory muscle strength in the early phase. Previous studies have suggested that respiratory muscle weakness also occurs in the early course of the disease (7, 8). The presence of respiratory muscle weakness in ambulatory patients with MS has also been shown previously (9–11), but studies investigating respiratory muscle strength in patients with MS with no–minimal disability are limited.

It is well known that respiratory muscle weakness results in a restrictive pulmonary defect in neuromuscular diseases. In the advanced stage of the disease vital capacity decreases when there is a 50% or greater loss of respiratory muscle strength (12). It is well established that pulmonary function is impaired in patients with MS with a relatively mild neurological impairment (13). However, there is a lack of information about whether spirometric pulmonary function is affected in fully ambulatory patients with MS who have respiratory muscle weakness.

Evaluation of functional exercise capacity using the six-minute walk test (6MWT) is a means of disability assessment that is commonly used in pulmonary and cardiac diseases (14). Goldman et al. (15) showed that the 6MWT is a feasible, reproducible and reliable measure of functional exercise capacity in patients with MS, and test–retest reliability intraclass correlation (ICC) for the 6MWT is 0.96 (16). The evaluation of functional exercise capacity using the 6MWT is becoming a commonly used outcome measure in the MS population. Although studies have shown that the distance walked during the 6MWT is severely decreased in ambulatory patients with MS (11, 15, 17), little is known about functional exercise capacity in patients with MS with no–minimal disability (Expanded Disability Status Scale (EDSS) 0–2.5). Few studies have investigated the differences in functional exercise

capacity in fully ambulatory patients with MS with different disability levels or the determinants of functional exercise capacity (15, 17).

Therefore, the aims of this study were to compare functional capacity, pulmonary function, and respiratory muscle strength in patients with MS with different disability levels and healthy controls, and to elucidate the determinant factors of functional exercise capacity in fully ambulatory patients with MS (EDSS = 0–4.5).

Our first hypothesis was that functional exercise capacity and respiratory muscle strength are reduced and pulmonary function is impaired in patients with MS with no–minimal disability compared with healthy controls. The second hypothesis was that spirometric pulmonary function is affected in fully ambulatory patients with MS with respiratory muscle weakness. The third hypothesis was that functional exercise capacity, respiratory muscle strength, and pulmonary function are more highly impaired in patients with mild–relatively severe disability compared with patients with no–minimal disability and healthy controls.

MATERIAL AND METHODS

Patients

A total of 43 fully ambulatory patients with MS (8 males, 35 females) referred from the outpatient clinic of the university hospital, during January 2010 to December 2010, and 30 sedentary, age- and sex-matched healthy controls (9 males, 21 females) were included in the study. Patients were classified into two groups according to the severity of their disability, using EDSS (18). EDSS is a method of quantifying disability in MS in 8 functional systems. EDSS scores 1.0–4.5 refer to patients with MS who are fully ambulatory, and scores 5.0–9.5 are defined by impairment to ambulation. There were 23 patients in Group I (EDSS: 0–2, no–minimal disability) and 20 in Group II (EDSS: 2.5–4.5, mild–relatively severe disability). Patients had clinically definite MS (19), were stable, and had no change in their medication over the last 3 months. Patients with recent viral infections, history of respiratory, orthopaedic, cardiovascular, or any other disease that would affect functional exercise capacity were excluded. The study was approved by the ethics committee of the university, and performed in accordance with the Declaration of Helsinki. Written informed consent to participate in the study was obtained from all patients. Patients' clinical evaluation was carried out by neurologists (BN, CI). Pulmonary function, respiratory muscle strength and functional exercise capacity were evaluated by physiotherapists (MB-G, AG-G) who were blind to the patients' disability level. All patients were evaluated at the same time in the morning, on separate days, by neurologists and physiotherapists. Clinical evaluations were carried out in the morning on the day of interferon beta-1a and 1b injections, and pulmonary function, respiratory muscle strength and functional exercise capacity were evaluated in the morning on the second day of injections**.**

Patients' and healthy controls' age, gender, height, body weight, and smoking behaviour were recorded. Patients' duration of illness and medications were also recorded.

Measurements

Pulmonary function tests. Spirometric measurement was performed using a portable spirometer (Spirobank MIR, Rome, Italy) according to the guidelines of the American Thoracic Society (20). The measurement was repeated 3 times and the highest value was recorded. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory flow from 25% to 75% ($FEF_{25–75\%}$) were expressed as percentages of the predicted values (21). A value of less than 75% of predicted FEV_1/FVC, or $FEF_{25–75\%}$, is classified as obstructive disease, and less than 75% of predicted FVC is classified as restrictive disease (20).

Respiratory muscle strength. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were assessed using an electronic pressure transducer (MicroRPM, Micromedical, Kent, UK). MIP was measured at residual volume; MEP was measured from total lung capacity, according to American Thoracic Society/European Respiratory Society (ATS/ERS) (22). Pressures were maintained for at least one second, and the highest technically satisfactory measurement was recorded (within 5%). Values were expressed as centimetres of water (cmH_2O). Reference values were used for comparison (23).

Functional exercise capacity. The 6MWT was applied in a 30-m unobstructed corridor according to the ATS (14). Patients and controls were instructed to walk at their normal pace, but to cover as great a distance as possible within 6 min. Standardized encouragement was given to the subjects at each minute. Subjects were allowed to stop and rest during the test, but were instructed to resume walking as soon as they were able to do so. The subject's heart rate was monitored during the test with a Polar heart rate monitor (PE3000 Polar Electro, Kempele, Finland). Maximum heart rate values obtained during the tests were recorded. The 6MWT distance was expressed as a percentage of predicted value (24). The 6MWT was repeated twice. Subjects rested for 30 min between tests, and the longest distance covered was recorded.

Pulmonary Index. The Pulmonary Index was used as a clinical predictor of respiratory dysfunction (25). The index comprises clinical signs, including cough as rated by an examiner, the patient's ability to count during a single exhalation, and the patient's report of a weak cough and difficulty clearing pulmonary secretions. The range of scores is 4–11, with a higher score indicating more highly impaired respiratory function.

Statistical analysis

All statistical analyses were performed using the statistical package SPSS 15.0 (SPSS Inc., USA). Data normality was tested using the Kolmogorov-Smirnov test. Data are expressed as means and standard deviations (SDs) unless otherwise stated. The clinical characteristics of the 3 groups were compared using analysis of variance (ANOVA). *Post-hoc* multiple comparisons were carried out using a Tukey test. Nominal data were compared using a χ^2 test. Since EDSS, Pulmonary Index, and disease duration data were not normally distributed, comparisons were performed using a Mann-Whitney *U* test. The correlations between 6MWT distance and demographic and clinical characteristics were calculated using Pearson's and Spearman's rank correlation coefficients, as appropriate. To determine the best predictor of exercise tolerance in MS, stepwise multiple regression analysis was performed with sex, age, anthropometry, EDSS, or heart rate as potential independent variables. Another multiple regression analysis was performed to determine the predictors of MIP with EDSS and age. A *p*-value less than 0.05 was considered statistically significant, unless otherwise stated.

RESULTS

A total of 73 patients with MS were evaluated for entry to the study, 30 patients were excluded for a variety of reasons; 5 had logistic problems, 12 declined to participate, and 13 did not meet the inclusion criteria (EDSS > 4.5). All patients had the relapsing-remitting type of MS, the median EDSS scores were 1.0 in Group I (min–max = 1–2) and 3.5 in Group II (min–

Table I. *Baseline demographic characteristics of patients with multiple sclerosis (MS) and healthy controls*

Characteristics	MS (EDSS 0–2)	MS (EDSS 2.5–4.5)	*p*	Healthy controls	MS (EDSS 0–2) vs controls *p*	MS (EDSS 2.5–4.5) vs controls *p*
Age, years, mean (SD)	33.30 (6.31)	38.15 (8.31)	0.29	34.50 (13.67)	0.91	0.45
Males/females, *n* (%)	5/18 (21.74/78.26)	3/17 (15/85)	0.57	9/21 (30/70)	0.55	0.32
Disease duration, years, mean (SD)	3.76 (3.45)	6.43 (4.65)	0.04			
Weight, kg, mean (SD)	61.00 (10.23)	66.71 (13.32)	0.20	65.47 (12.92)	0.95	0.28
Height, cm, mean (SD)	165.48 (8.11)	164.95 (7.27)	0.97	164.1 (7.58)	0.81	0.93
BMI, kg/m^2, mean (SD)	24.71 (4.58)	22.47 (3.64)	0.27	24.83 (5.32)	0.97	0.19
Smoking, pack-years, mean (SD)	4.26 (5.36)	9.68 (14.28)	0.10	2.24 (4.34)	0.67	0.009*
Smoking, non/current/ex-smoker, *n* (%)	10/11/1 (43.5/47.8/8.7)	10/9/1 (50.0/45.0/5.0)		20/2/8 (66.7/6.7/26.7)		

*$p < 0.05$.
SD: standard deviation; BMI: body mass index; EDSS: Expanded Disability Status Scale.

max = 2.5–4.5). Patients were on optimal medical treatment, including interferon beta-1a (15 patients per group (65.22%, 75%, respectively)) and interferon beta-1b (6 patients (26.08%) in Group I, and 4 patients (20%) in Group II), 3 times a week. There was no significant difference in medication in terms of dose and injection frequency between the groups ($p > 0.05$). Fourteen patients per group (60.87% for Group I and 70% for Group II) used corticosteroids for at least one year prior to the study. There were no significant differences between the 3 groups in terms of the demographic characteristics age, gender, weight, height, and body mass index (BMI) ($p > 0.05$). The duration of disease was longer in Group II compared with Group I (Table I). Five patients (21.74%) in Group I and 7 (35%) in Group II reported a history of difficulty handling mucus. All patients' coughs were normal and no patients reported resting dyspnoea, orthopnoea or dysphagia. Ten patients (43.48%) in Group I and 8 (40%) in Group II reported dyspnoea on exertion. Ten patients (43.48%) in Group I and 11 (55%) in Group II reported fatigue while resting.

Pulmonary function

Four patients in Group I (17.39%) and 2 (10%) in Group II had less than 75% of predicted FEV_1/FVC; 6 patients in Group I (26.09%) and 10 in Group II (50%) had less than 75% of predicted PEF; and 8 patients per group (34.78% and 40%, respectively) had less than 75% of predicted $FEF_{25–75\%}$. The percentage of predicted PEF was significantly lower in Group II compared with controls ($p < 0.05$, Table II).

Inspiratory and expiratory muscle strength

The MIPs of 11 patients in Group I (47.83%) and 17 in Group II (85%) were lower than the 95% confidence interval (95% CI) of the healthy controls (102.39–118.70 cmH_2O). The MEPs of 18 patients in each group (78.26% Group I, 90% Group II) were lower than the 95% CI of the healthy controls (131.25–168.12 cmH_2O). Seven patients in Group I and II (30.43%, 35%, respectively) had a %MIP below 80% predicted, 19 patients in Group I (82.61%) and 18 (90%) in Group II had a %MEP below 80% predicted. Although MIP, %MIP, MEP and %MEP were lower in Group I compared with healthy controls, only the difference in MEP and %MEP were statistically significant ($p < 0.05$). MIP, MEP, %MIP and %MEP were significantly lower in Group II compared with healthy controls ($p < 0.05$). MIP, MEP, %MIP and %MEP were similar in MS groups (Table II). Ten patients with MS out of a total of 43 (23.26%) had a %MEP below 50% predicted and

Table II. *Comparison of pulmonary function, respiratory muscle strength and Pulmonary Index in patients with multiple sclerosis (MS) and controls*

Characteristics	MS (EDSS 0–2) Mean (SD)	MS (EDSS 2.5–4.5) Mean (SD)	*p*	Healthy controls Mean (SD)	MS (EDSS 0–2) and controls *p*	MS (EDSS 2.5–4.5) and controls *p*
FEV_1, %	98.22 (14.59)	97.15 (11.18)	0.95	98.53 (9.43)	0.99	0.91
FVC, %	105.39 (12.16)	101.95 (14.17)	0.65	99.53 (11.93)	0.22	0.77
FEV_1/FVC	82.14 (8.81)	83.51 (6.37)	0.87	87.34 (10.18)	0.09	0.28
PEF, %	87.65 (24.51)	78.75 (15.74)	0.28	99.57 (15.39)	0.06	0.001*
$FEF_{25–75\%}$	79.13 (20.57)	79.95 (16.29)	0.99	86.97 (17.71)	0.27	0.39
MIP, cmH_2O	97.76 (28.36)	84.00 (17.06)	0.14	110.56 (21.44)	0.13	0.001*
MIP, % predicted	103.72 (30.85)	94.75 (25.65)	0.51	112.68 (20.45)	0.44	0.05*
MEP, cmH_2O	112.43 (23.33)	98.89 (27.81)	0.49	149.69 (48.45)	0.002*	<0.001*
MEP, % predicted	66.57 (11.82)	60.89 (13.32)	0.40	83.56 (15.36)	<0.001*	<0.001*
Pulmonary Index (4–11)	4.21 (0.08)	4.35 (0.11)	0.34			

*$p < 0.05$.
FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; $FEF_{25–75\%}$: forced expiratory flow from 25% to 75%; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

a FVC% significantly lower compared with the remaining 33 patients (107.13 ± 12.34% vs 95.40 ± 12.14%, $p = 0.18$).

Functional exercise capacity

The 6MWT distance covered by 17 patients (73.91%) in Group I (min–max = 555.97–608.43 m) and 20 patients (100%) in Group II (min–max = 403.57–489.23 m) were lower than the 95% CI of the healthy controls (min–max = 618.64–678.17 m). The 6MWT distance was less than 80% of the predicted value in 5 patients (21.74%) in Group I and 17 (85%) in Group II. The distance covered during the 6MWT and %6MWT was significantly shorter in Group II compared with Group I. The distance covered during the 6MWT and %6MWT was significantly shorter in Group I and II compared with healthy controls (Table III). Heart rate was similar in MS groups and healthy controls before the 6MWT ($p > 0.05$). Heart rate increased significantly in Group I compared with Group II and controls.

Pulmonary Index score

Pulmonary Index scores were similar in both MS groups (Table II). Five patients (21.74%) in Group I and 7 (35%) in Group II scored 5 points on the Pulmonary Index. Three patients in Group I (13.04%) and 5 (25%) in Group II reported a history of difficulty handling mucus/secretions, and two patients in each group (8.70% and 10%, respectively) were unable to count to 30 on a single exhalation.

Correlations and regression analysis

The 6MWT distance was significantly correlated with age, gender, EDSS ($r = –0.730$, $p < 0.001$), height, MEP ($p = 0.07$), and heart rate change during 6MWT ($p < 0.05$, Table IV). Percentage predicted 6MWT distance was significantly correlated with weight, BMI, EDSS ($r = –0.717$, $p < 0.001$), MIP, and heart rate change during 6MWT ($p < 0.05$, Table IV). The 6MWT distance was not significantly correlated with smoking, Pulmonary Index and pulmonary function ($p > 0.05$). EDSS was significantly correlated with age, disease duration, PEF ($r = –0.320$, $p = 0.036$), MIP, MEP and change in heart rate during 6MWT ($p < 0.05$, Table IV). The MIP and MEP were not significantly correlated with disease duration ($p > 0.05$). In the multiple regression analysis conducted in the 43 patients with MS, 75% of the variance in the 6MWT distance was explained by the EDSS ($R^2 = 0.55$, $p < 0.001$), change in heart rate during 6MWT ($R^2 = 0.06$, $p = 0.007$), age ($R^2 = 0.05$, $p = 0.009$), and gender ($R^2 = 0.09$, $p = 0.003$). When the 6MWT distance was expressed as a percentage of predicted value, 64% of the variance in the 6MWT distance was explained by EDSS ($R^2 = 0.55$, $p < 0.001$) and change in heart rate during 6MWT ($R^2 = 0.09$, $p = 0.002$). In the multiple regression analysis conducted in the 43 patients with MS, 20% of the variance in the MIP was explained by the EDSS ($R^2 = 0.10$, $p < 0.006$) and age ($R^2 = 0.10$, $p = 0.032$).

Table IV. *Correlations between functional capacity and demographic characteristics, Pulmonary Index, heart rate and respiratory muscle strength in patients with multiple sclerosis*

	6MWT m		6MWT % predicted		EDSS	
Characteristics	*r*	*p*	*r*	*p*	*r*	*p*
Age, years	–0.59	<0.001*	–0.14	0.36	0.41	0.006*
Gender	–0.35	0.02*	–0.14	0.37	0.07	0.64
Weight, kg	0.23	0.15	0.41	0.006*	–0.23	0.14
Height, cm	0.41	0.006*	0.14	0.39	–0.06	0.69
BMI, kg/m^2	0.03	0.86	0.37	0.01*	–0.24	0.12
Pulmonary Index (4–11)	–0.16	0.30	–0.28	0.06	0.25	0.10
Disease duration, years	–0.23	0.13	–0.26	0.09	0.48	0.001*
MIP, cmH_2O	0.21	0.20	0.33	0.03*	–0.32	0.04*
MIP, % predicted	–0.06	0.69	0.20	0.21	–0.21	0.19
MEP, cmH_2O	0.28	0.07	0.24	0.14	–0.31	0.05*
MEP, % predicted	–0.07	0.68	0.05	0.74	–0.15	0.37
Δ Heart rate, bpm	0.69	<0.001*	0.75	<0.001*	–0.65	<0.001*

*$p < 0.05$.
6MWT: six-minute walk test; EDSS: Expanded Disability Status Scale; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; $FEF_{25–75\%}$: forced expiratory flow from 25% to 75%; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; bpm: beats/min.

DISCUSSION

The main findings of the present study are that respiratory muscle strength, and functional exercise capacity are reduced, and pulmonary function is affected even in patients with MS with no–minimal disability. Ambulatory patients with multiple sclerosis who have a higher level of disability have lower pulmonary function, respiratory muscle strength and functional

Table III. *Comparison of functional capacity and heart rate of patients with multiple sclerosis (MS) and healthy controls*

Characteristics	MS (EDSS 0–2) Mean (SD)	MS (EDSS 2.5–4.5) Mean (SD)	*p*	Healthy controls Mean (SD)	MS (EDSS 0–2) and controls *p*	MS (EDSS 2.5–4.5) and controls *p*
6MWT, m	582.20 (60.66)	446.40 (91.52)	<0.001*	648.41 (79.71)	0.009*	<0.001*
6MWT, % predicted	85.98 (9.19)	67.31 (11.21)	<0.001*	98.08 (13.29)	0.001*	<0.001*
Heart rate, beats/min, before 6MWT	83.04 (11.66)	86.25 (11.08)	0.64	87.13 (11.81)	0.41	0.96
Heart rate, beats/min, after 6MWT	137.17 (16.16)	116.10 (19.56)	0.004*	130.03 (24.25)	0.43	0.05*
Δ Heart rate, beats/min	54.13 (16.17)	29.85 (14.70)	<0.001*	42.90 (20.04)	0.06	0.03

*$p < 0.05$.
SD: standard deviation; 6MWT: six-minute walk test.

capacity than less disabled ones and controls. Expiratory muscles are weakened earlier and to a greater extent than inspiratory muscles. Forced vital capacity is decreased in fully ambulatory patients with MS who have a %MEP below 50% predicted. Neurological disability level, heart rate difference on exertion, age and gender are the determinants of functional exercise capacity, and 75% of walking distance was explained by these variables.

Previous non-controlled (5–7, 26) and controlled (8, 27) studies have shown respiratory muscle weakness in patients with MS with advanced disability. A controlled study showed respiratory muscle weakness in mildly disabled (median EDSS 2.09 ± 0.2, range 0–6.5) patients with MS (28). To our knowledge, the present study is the first to demonstrate weakness of inspiratory (47.83%) and expiratory (78.26%) muscles in the very early course of the disease, especially in patients with no–minimal disability. In addition, expiratory muscle weakness in patients with mild–relatively severe disability (90%) is more prominent compared with less disabled (78.26%) patients. This study documents the changes in respiratory muscle strength at the EDSS 0–2 score level, but other studies have documented this at the 2.5–10 level. Garland et al. (29) showed that central motor conduction to the diaphragm is abnormal in patients with MS who have mild–moderate disability. This may partially explain why inspiratory muscle weakness is seen in patients with MS. In accordance with previous studies we showed that expiratory muscles are weakened earlier and to a greater extent (5, 6, 11, 30) than inspiratory muscles. Our findings are consistent with previous studies suggesting that the paralysis in MS ascends, starting in the lower extremities, and moving to the expiratory muscles, with the intercostal muscles and the diaphragm being the last to be affected (5, 25).

We showed that EDSS is correlated with MIP, MEP, and 20% of the variance in the MIP is explained by the patient's disability status. These results emphasize that, as MS worsens, the inspiratory muscles weaken. Longitudinal studies are needed to investigate the course of respiratory muscle weakness. Similar to Savci et al. (11), we also demonstrated that there is no correlation between respiratory muscle strength and duration of the disease, in contrast to Foglio et al. (7). Others factors, such as disease duration, drugs such as steroids, inactivity, deconditioning, and oxidative stress may contribute to respiratory muscle weakness (31). Further studies are needed to investigate the effects of these factors on respiratory muscle strength.

This is the second study to document changes in 6MWT in patients at the EDSS 0–2 score level, but other studies have documented 6MWT at the 2.5–6.5 level. Similar to Goldman et al. (15), we showed that functional exercise capacity, evaluated using 6MWT, is severely impaired in patients with mild–relatively severe disability compared with patients with no–minimal disability. In the present study 73.91% of the patients with no–minimal disability and 100% of the patients with mild–relatively severe disability walked shorter distances than the 95% CI of the healthy controls (mean 618.64 m). Chetta et al. (32) showed a significant decrease in 6MWT distance in 11 patients with MS (EDSS = 1–3.5) compared with 10 healthy controls. The study conducted by Savci et al. (11) also showed that the 6MWT distance was shorter in 30 ambulatory patients with MS (EDSS < 6.5) compared with 30 healthy controls. Goldman et al. (15) compared the 6MWT distance for patients with MS (with mild, moderate, severe disability) with healthy controls, and reported that patients walked shorter distances. Gijbels et al. (17) showed that patients with moderate disability ($n = 21$, EDSS = 4.5–6.5) covered shorter distances than those with mild disability ($n = 29$, EDSS = 1.5–4). Weltzel et al. (33) and Pfalzer & Fry (34) reported more impaired functional exercise capacity in patients with MS who are more disabled compared with our findings. These findings support our finding that, as the disability worsens, functional exercise capacity decreases in patients with MS.

In the present study, 75% of the variance in the 6MWT distance was explained by the disability status, heart rate difference during 6MWT, age and gender. These findings suggest that patients with MS with higher disability, lower heart rate while walking, advanced age and female gender result in more decreased functional capacity. Similar to our findings, Chetta et al. (32) and Savci et al. (11) showed that the distance walked during the 6MWT in patients with MS is related to disability status. Patients who were more disabled walked shorter distances, and therefore reached lower heart rate compared with less disabled in 6MWT. In accordance with the previous findings patients with no–minimal disability had higher exercise heart rates compared with healthy controls (11). Autonomic dysfunction involving the cardiovascular system in MS results in abnormal increases in heart rate (35).

Inconsistent with the results of previous studies (5, 6, 13), we showed that pulmonary function evaluated using spirometry was affected in fully ambulatory patients with MS. Pulmonary function test results were similar, except for PEF, in MS groups and healthy subjects. Obstructive type pulmonary function abnormality (decreased FEV_1/FVC or $FEF_{25–75\%}$) was prevailing in 52.17% of patients with MS with no–minimal disability, and 50% of patients with mild–relatively severe disability. None of the patients demonstrated restrictive pulmonary function abnormality. Fry et al. (9) reported less (43.5%) obstructive type abnormalities in non-smoking patients with MS than our findings. These abnormalities may be due to cigarette smoking in patients with MS. Savci et al. (11) demonstrated that PEF is lower in patients who are more disabled compared with healthy controls, as we did, which may be due to the weakened expiratory muscles in patients with MS.

A previous study showed that patients with MS with an EDSS score > 5.5 have higher probability of having impaired cough (36). Gosselink et al. (37) reported higher Pulmonary Index scores in patients who are more disabled. Although we clearly showed that respiratory muscles were affected even in the early phase of MS, the degree of respiratory dysfunction evaluated using the Pulmonary Index was low. Small numbers of patients reported a history of difficulty handling mucus/secretions, and a single exhalation could not be considered. The findings reported by our patients may be early signs of pulmonary dysfunction and encourage us to start respiratory

muscle training at the onset of the disease long before the disability worsens.

Limitations

Patients were predominantly female, and volitional methods were used for the measurement of respiratory muscle strength. Non-volitional methods may reflect the dysfunctions more accurately.

Maximal voluntary inspiratory and expiratory pressures (MIP and MEP) are probably the most frequently reported non-invasive estimates of respiratory muscle strength. Black & Hyatt (23) reported this non-invasive technique and reference equations, which has been widely used in patients, healthy control subjects across all ages, and in athletes (38). It would be better to use the reference values for respiratory muscle strength for the population studied in this study; however, there are no values reported in literature. Factors, for example inactivity, that might affect functional exercise capacity in patients with MS should be investigated further.

Conclusion

Although respiratory muscle weakness begins in the early course of MS, it is not recognized until the later stages. The results of this study show that respiratory muscle weakness, especially expiratory muscle weakness, is common in patients with MS with no–minimal disability, as well as in those with mild–relatively severe disability. Routine measurement of respiratory muscle strength in patients with MS is recommended for the early detection of weakness. Rehabilitation programmes that include respiratory muscle training may prevent the occurrence of respiratory complications. Aerobic exercise training should be started in the early course of the disease in order to improve functional exercise capacity in patients with MS.

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