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Respiratory muscle function and exercise capacity in multiple sclerosis

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ABSTRACT: Patients with multiple sclerosis (MS) show a poor exercise tolerance. A reduction in respiratory muscle strength has also been reported. The purpose of this study was to evaluate whether reduction in exercise tolerance was related to respiratory muscle dysfunction.

Twenty four multiple sclerosis patients (mean±SD age: 48±9 yrs, duration of illness 12.2±6 yrs, severity of illness as assessed by Expanded Disability Scale Score (EDSS) 5.3±2), underwent detailed evaluation of lung function tests, arterial blood gas analysis, respiratory muscle strength and endurance, and exercise test on an arm ergometer.

Sixteen of the 24 patients were able to perform the exercise test (Group I), whilst the other eight were not (group II). Arterial blood gases and lung function tests were normal for both groups. Respiratory muscle strength as assessed both by maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) was significantly reduced (MIP 18–76 cmH_2O; MEP 16–82 cmH_2O) compared to predicted values. Inspiratory muscle endurance time was significantly reduced in Group II in comparison to Group I (247±148 *vs* 397±154 s, respectively). Both MIP and MEP were significantly related to inspiratory muscle endurance time. Endurance time, MIP and MEP were inversely significantly related to duration of illness, whilst only endurance time was significantly related to Expanded Disability Scale Score. Exercise test on arm ergometer as assessed by maximal oxygen consumption ($\dot{V}O_2max$) (11±2 $ml \cdot kg^{-1}$= 42% pred), maximal workload (Wmax) (22.6±6.8W) and maximal heart rate (HRmax) (73±11 51% pred) was reduced. $\dot{V}O_2max$ and HRmax were slightly, but significantly, related to endurance time. Wmax was significantly related to MIP.

We conclude that, in patients with multiple sclerosis, reduction in exercise tolerance may be related, at least partially, to respiratory muscle dysfunction.

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Multiple sclerosis (MS) is a demyelinating disease affecting the motor pathways, which causes lesions widely in the central nervous system, and which may be complicated by acute respiratory failure, and events such as atelectasis, pneumonia and diaphragmatic weakness [1–4]. However, the involvement of the respiratory function has so far not been thoroughly assessed. Whilst, as a whole, respiratory function has been found normal in these patients, a reduction in respiratory muscle (RM) strength has been reported [5–7]. Patients with MS show a poor exercise tolerance, with fatigue and dyspnoea on exertion, that limits the activity of daily living [8, 9]. High energy cost of walking has been suggested to be an important contributing factor to breathlessness and leg fatigue in these patients [10]. Exercise tolerance has been shown to be related, at least partially, to spirometric values and to RM function, both in normal and in pathological conditions [11–13]. No information regarding this is available for patients with MS.

The aim of this study was to assess whether RM dysfunction, a condition partially reversible with adequate training [12, 14, 15], may play a role in reducing exercise capacity in these patients.

Methods

Twenty four patients (17 females and 7 males; mean±SD age: 48±9 yrs; weight 65±12 kg; Height 166±9 cm), consecutively referred to our laboratory for routine lung function tests, were studied. All patients met the criteria of POSER *et al*. [16] for the diagnosis of definite MS. Four of them were current smokers. All of the patients were admitted to the Department of Rehabilitation for a period of rehabilitation therapy and scheduled clinical assessment. None of them was in a period of relapse. All the patients had undergone one or more periods of high dose steroid therapy (dexamethasone 64 mg daily)

in the course of the illness, but none was currently in therapy or had been treated for at least three months preceding the study. All gave their informed consent to participate in the study, which was approved by the Ethics Committee of Clinica del Lavoro Foundation.

Clinical assessment

All the patients underwent a complete neurological examination, clinical and laboratory assessment of disability by means of Expanded Disability Status Scale (EDSS) and functional System (FS) [17, 18]. Patients with a clinical, instrumental or laboratory supported suspicion of other neurological or systemic diseases were excluded. The EDSS provides a score ranging from zero, indicating normal neurological findings, to 10, indicating death from MS. FS yields extensive information on the grade of involvement of the following neurological functions: pyramidal, sensory, cerebellar, brain stem functions, sphincter and mental. The impairment was expressed with a score ranging from zero to 5 or 6; the higher the score the more involved the function. The EDSS gives a comprehensive measure of the disability. FS allows extremely different symptoms to be evaluated on the basis of the involvement of the main neurological functions. The EDSS score was assigned without knowledge of the subject's pulmonary and exercise test results.

Pulmonary function tests

Dynamic lung volumes were measured in the sitting posture by means of a pneumotachograph with volume integrator (Medical Graphic Corp., St. Paul MN, USA). Static volumes were measured by means of a plethysmograph (Medical Graphic Corp., St. Paul MN, USA). Diffusion capacity of the lungs for carbon monoxide (DLCO) was measured by means of the "single breath" method (Diffusion Star FG90, Basel, Switzerland). Gas analysis was performed using an automated analyser (ABL 300, Radiometer, Copenhagen, Denmark) on blood samples drawn from the radial artery. The prediction equations of QUANJER [19] were used for sex, age, height, normal lung volumes and DLCO.

Respiratory muscle function

RM strength was assessed by measuring maximal static inspiratory and expiratory pressures (MIP and MEP, respectively) according to the method of BLACK and HYATT [20] using a respiratory module system (RPM, Medical Graphics Corp., St. Paul MN, USA). The RPM consists of a pressure transducer, a waveform analyser and a pneumatic control system. The effective measurement range was ±14.7 kPa (155 cmH_2O). The subjects, whilst comfortably seated and wearing a noseclip, performed maximal inspiratory and expiratory efforts, starting from functional residual capacity (FRC) and total lung capacity (TLC), respectively, against an obstructed flanged mouthpiece with a small air leak to prevent glottic closure. The subjects were verbally encouraged to achieve maximal strength. The determinations were repeated until five measurements, varying by <5% and sustained for at least 1 s, were obtained: the best value achieved was considered in data analysis. MIP and MEP were expressed as absolute values and as percentage of the predicted values by BRUSCHI *et al*. [21].

Endurance of inspiratory muscles was measured, using the modified procedure of GROSS *et al*. [15], in sitting posture. The patients were taught to breathe through a series of inspiratory resistances of a device widely used for resistive breathing training (PFlex(R)) connected to a manometer, setting the dial selector at a resistance able to elicit a mouth pressure of 70% of their MIP (target pressure). During the test, inspiratory pressure at the mouth (Pm) was measured and displayed on a monitor oscilloscope, and the patient was asked to maintain the target pressure. Expiration was unloaded and each patient was free to choose his respiratory rate. The endurance time was determined when the patient was not able to sustain the target pressure for longer than three consecutive breaths. Endurance time was expressed in seconds and used to find correlations with RM strength, lung function and exercise tolerance.

Exercise test

Patients were submitted to a symptom limited exercise test on an arm ergometer [22] under electrocardiographic control. The arm cycle ergometer was positioned so that the subjects could use the arm-crank sitting upright, with the feet flat on the floor. It was recommended that the ergometer be adjusted so that the mid-point of the sprocket wheel was at shoulder level. During cranking, the arms were to be extended at right angles to the body at maximal capacity, allowing for a slight bend at the elbow, analogous to the lower limb extension in leg cycling, to facilitate maximum mechanical efficiency. After stabilization and a 2 min warm-up period, the load was increased by 12.5 W every 3 min (maintaining cranking rate of 50–60 rpm) until exhaustion. At baseline and every 30 s, oxygen consumption ($\dot{V}O_2$), respiratory (RR) and heart rate (HR), minute ventilation ($\dot{V}E$), and blood pressure (BP) were recorded. Respiratory parameters were assessed by a CO_2/O_2 analysing system connected to a pneumotachograph (Ergostar FG 90, Basel, Switzerland).

Data analysis

The BMDP Statistical software analysing program was used to calculate mean and standard deviations of the measured parameters in all patients. A two-tailed t-test was used to compare results between patients able and unable to perform the exercise test. A linear regression analysis corrected for multiple comparison was performed to correlate lung, RM function, and exercise tests in patients able to perform the effort test: a level of $p<0.05$ was considered significant.

Results

The mean±SD duration of illness was 12.2±6 yrs, with a severity as assessed by a mean EDSS of 5.3±2. Most of the patients were ambulatory or required assistance for ambulation. All patients were able to perform lung function tests, evaluation of RM strength and endurance. Sixteen of the 24 patients were able to perform the arm exercise test (Group I). Eight of the 24 patients (Group II) were unable to perform the exercise test due to a lack of upper limb co-ordination. EDSS was significantly more compromised in Group II than in Group I 7±1 *vs* 5±2, $p<0.05$). Clinical neurological patterns as assessed by EDSS score and FS score are shown in figure 1.

Lung function

Blood gases were normal in all subjects (arterial oxygen tension (Pa_{O_2}) 8.9–13.4 kPa, and arterial carbon dioxide tension (Pa_{CO_2}) 4.2–5.6 kPa). Individual values of lung function tests in the whole group of patients are shown in figure 2. Lung function tests were normal for the whole group, no significant difference being found between the two groups.

Respiratory muscle function

Values of MIP and MEP as percentage of predicted value for each patient in the study are also shown in

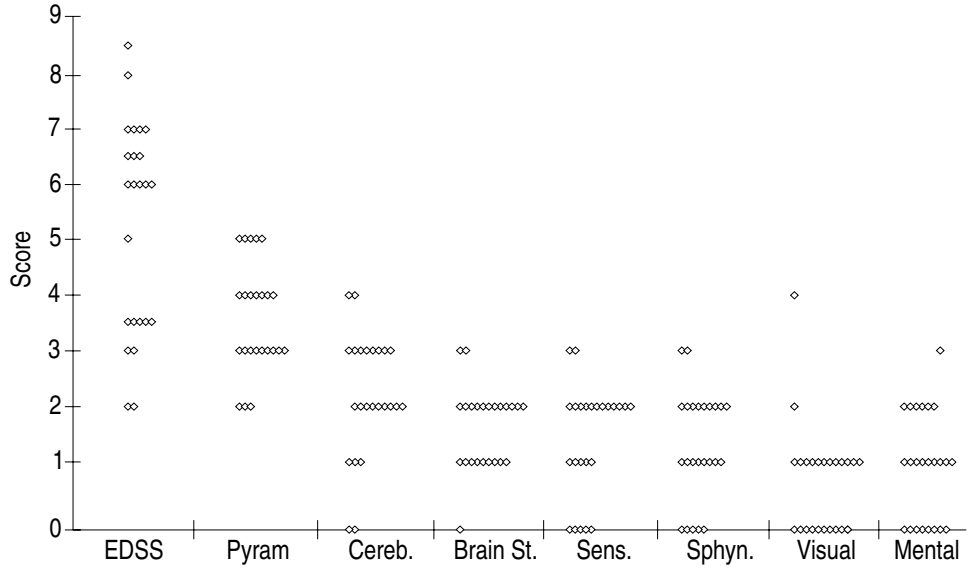

Fig. 1. – Level of neurological involvement as assessed by EDSS and Functional Systems for individual patients. EDSS: Expanded Disability Status Scale; pyram: pyramidal functions; cereb: cerebellar functions; brain st: brain stem functions; sens: sensory functions; sphin: bowel and bladder sphincter functions; visual: visual (or Optic) functions; mental: cerebral (or mental) functions.

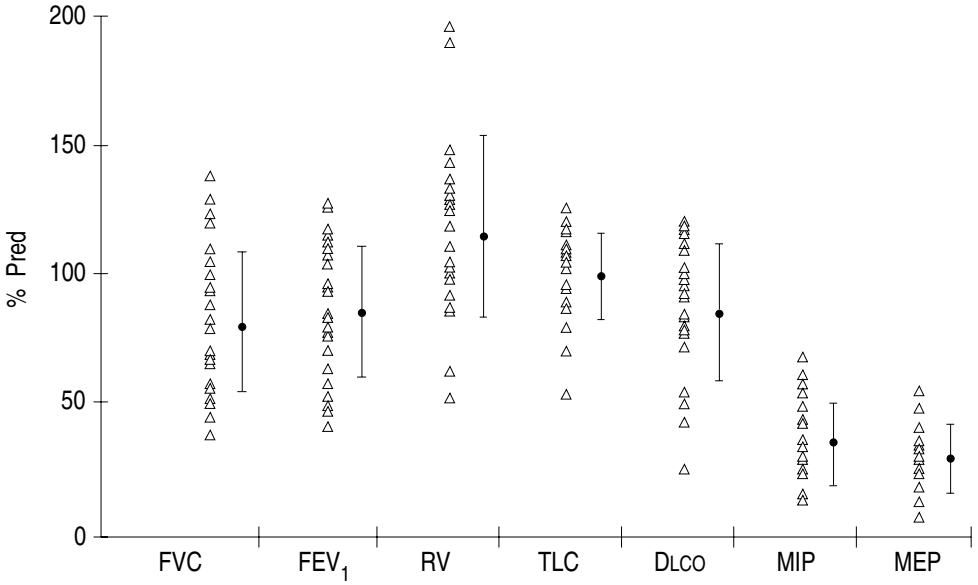

Fig. 2. – Lung function test and respiratory muscle strength (individual data). FVC: expiratory forced vital capacity; FEV_1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusion capacity of the lungs for carbon monoxide; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; % pred: percentage of predicted. Mean and standard deviation are indicated.

figure 2. RM muscle strength, as assessed both by MIP and MEP, was significantly reduced compared to predicted values in most of the patients of the whole group (MIP range 18–76 cmH_2O; MEP range 16–82 cmH_2O); patients unable to perform exercise test showing a more severe but nonsignificant reduction in comparison to patients able to perform exercise test. In all groups, MIP and MEP were highly correlated and similarly compromised. The relationship between individual values of MIP and vital capacity (VC) in all subjects are shown in figure 3. MIP and VC were weakly significantly correlated. Endurance time was significantly reduced in Group II in comparison to Group I (247±148 *vs* 397±1545, respectively. Both MIP and MEP were significantly correlated with endurance time (r 0.50 and 0.55, respectively, p<0.01). No significant relationship was found between spirometric values, RM function tests, and duration of illness. In all the patients, MIP and MEP were weakly and inversely significantly related to duration of illness (r -0.43 and -0.41, respectively, p<0.05) but not with EDSS. Endurance time was significantly related to both EDSS and duration of illness (r -0.72, p<0.01; and r -0.44, p<0.05, respectively).

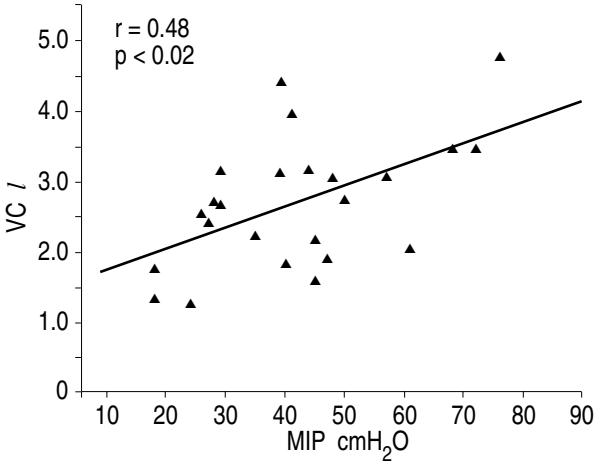

Fig. 3. – Relationship between individual absolute values of maximal inspiratory pressure (MIP) and vital capacity (VC) in the patients studied.

Exercise tolerance

Table 1 shows the results of the arm effort test. Only basal HR was correlated to EDSS. All patients able to perform an exercise test stopped it due to a sense of muscle fatigue. Exercise capacity as assessed by Wmax performed, $\dot{V}O_2$max and HRmax was reduced. $\dot{V}O_2$max and HRmax were slightly, but significantly, related to endurance time but not to MIP. In contrast, Wmax, another index of exercise capacity, was significantly related to MIP. Basal RR was inversely significantly related to endurance time and MEP.

Discussion

This study, on a small number of patients, confirms the occurrence of a reduction in both inspiratory and expiratory muscle function in ambulatory patients with MS. This study also confirms that exercise capacity in these patients is reduced. The reduction in exercise capacity is related more to inspiratory muscle function than to the severity of neurological compromise as assessed by EDSS.

The degree of severity of the disease of our patients was less than in other studies [6], as assessed by an average EDSS of 5.3, and by the fact that all patients were ambulatory with or without assistance. On the other hand, the duration of illness was longer in our patients (12.2 yrs). The static and dynamic volumes of our patients were in the range of normality. The literature reports essentially normal values in the populations studied [5–7, 10].

Table 1. – The Pearson correlation relationship between working capacity parameters and endurance, EDSS, MIP and MEP

			Pearson correlations			
	Mean	SD	Endurance r	EDSS r	MIP r	MEP r
Work capacity Wmax	22.6	6.8	0.36	-0.30	0.49**	0.37
$\dot{V}O_2$ basal ml·min^{-1}	239.1	38.1	-0.04	-0.04	-0.04	-0.06
$\dot{V}O_2$max ml·min^{-1}	711.2	151.6	0.56**	-0.26	0.07	0.3
$\dot{V}O_2$max·kg^{-1} ml·min^{-1}kg^{-1}	11.2	2	0.52*	-0.27	0.10	0.28
RR basal breath·min^{-1}	17.3	2.4	-0.40*	0.31	0.26	-0.57**
RRmax breath·min^{-1}	26.1	6.6	0.12	-0.04	0.10	-0.02
$\dot{V}_E$ basal *l*·min^{-1}	10.8	1.4	-0.02	0.15	-0.16	0.23
$V_E$max *l*·min^{-1}	30.7	9.5	0.33	0.12	-0.03	0.24
HR basal beats·min^{-1}	78.5	9.7	0.35	0.49**	-0.04	-0.11
HRmax beats·min^{-1}	125.7	15.7	0.45**	-0.26	0.30	0.28
HRmax % % pred	73	11	0.51*	-0.31	0.33	0.30

The statistical significance of the correlations are also presented. *: p<0.05; **: p<0.01. $\dot{V}O_2$: oxygen consu-mption; RR: respiratory rate; V_E: minute ventilation; HR: heart rate; MIP and MEP: maximal inspiratory and expiratory pressure, respectively; EDSS: Expanded Disability Status Scale.

Respiratory muscle function

MIP and MEP, indices of RM strength were reduced to a similar extent. Similar results were found by OLGIATI *et al*. [10]. In contrast, SMELTZER *et al*. [6], in patients with a relatively more severe disease, found MEP values similar to ours, but MIP was less compromised than in our patients. The predicted values of MIP and MEP that we used were those of BRUSCHI *et al*. [21], whilst those of BLACK and HYATT [20] were used by Smeltzer *et al*. Our patients performed five manoeuvres in comparison to the three performed by the patients of Smeltzer's *et al*., and the highest (more negative) was recorded. The number of repetitions of the MIP manoeuvre may influence the results by enhancing the learning factor [23]; theoretically, a greater number of repetitions inducing a better (higher) value in MIP. Taking this into consideration, the results of MIP found in our study appear, in fact, to be really lower than those of Smeltzer *et al*. Differences in duration of illness might explain our reduced levels of MIP in comparison to those of Smeltzer *et al*.; in fact, in both studies MIP values were inversely related to the duration of illness, which was longer in our study. Interestingly, statistical analysis showed that MIP and MEP were not related to EDSS, which was more compromised in the study of Smeltzer *et al*. Differences in motivation, learning, or method of performing the manoeuvre might also explain this difference, although the variations between different studies may largely be explained by the very variable nature of the condition.

Myopathy involving respiratory muscles is a well-known side-effect of corticosteroid therapy [24]. None of our patients showed a clinically overt myopathy or changes in muscle enzymes during the period of the study, or in the course of the illness, and none of the patients was receiving corticosteroid therapy during, or in the period preceding, the study. However, we cannot exclude a subclinical involvement of both limb and respiratory muscles due to their former steroid therapy.

Measurement of endurance time is performed differently in the literature [25]. We used a modified method according to GROSS *et al*. [15], who measured the lowest value of inspiratory mouth pressure sufficient to produce fatigue, whilst we measured endurance time. A limitation of this measurement is that we have no control values. Nevertheless, although we cannot state that the values of endurance time of our patients were low, the close relationship with the reduced values of both MIP and MEP led us to infer that this parameter was reduced in our patients. Furthermore, our main purpose was not to assess the absolute levels of endurance time but to evaluate a relationship between this parameter and exercise tolerance. Our patients were allowed to breathe with their own respiratory pattern, and this fact may be criticized, although MORRISON *et al*. [26] have recently demonstrated that regulation of breathing frequency is unnecessary in the 2 min threshold loading test to obtain reproducible results for measures of respiratory endurance. A third limitation of this measurement may be the lack of electromyographic control, so that we cannot exclude central fatigue in terminating the run [27]. Nevertheless, for the limited purposes of our study, we think that our measurement of endurance time may give comparable results. The patients of SMELTZER *et al*. [6] showed a maximal voluntary ventilation (MVV) only minimally diminished (68% pred). MVV or its derivate indices, such as maximal sustained ventilatory capacity, is considered to be an index of inspiratory muscle endurance. Endurance time was inversely related both to EDSS and duration of illness, it was also closely correlated both with MIP and MEP. This result is in agreement with TANTUCCI *et al*. [7], who found a close correlation of MVV both with MIP and MEP.

Exercise tolerance

Exercise tolerance of our patients was compromised. On an arm effort test, their $\dot{V}O_2$max and HRmax were reduced. Reduced $\dot{V}O_2$max in MS patients was reported by BJURO *et al*. [28] at 16 ml·kg^{-1}·min^{-1}; whilst OLGIATI *et al*. [10] extrapolated a mean $\dot{V}O_2$max of 30 ml·kg^{-1}·min^{-1}, which is far greater than the $\dot{V}O_2$max levels found in our study; both these studies having been performed on a treadmill. Differences in $\dot{V}O_2$max may be elicited by the way of performance of the exercise test [22, 29, 30]. Although our patients were ambulatory, we preferred to perform an arm effort test, since most of our patients were not able to cope with a treadmill. The severity of disease in the patients of OLGIATI *et al*. [10] is not known, and it is not comparable to the EDSS applied to our patients. Reproducibility and sensitivity of arm exercise test is widely recognized in patients with musculoskeletal problems, where attainment of true HRmax and $\dot{V}O_2$max may not be possible with conventional leg exercise testing [22]. Although, at a given submaximal workload, arm exercise is performed at a greater physiological cost than leg exercise, $\dot{V}O_2$max obtained with an arm exercise in men generally varies between 64–80% of leg $\dot{V}O_2$max [22, 29]. In the light of this observation, our results in $\dot{V}O_2$max may show similar exercise capacity to the patients of BJURO *et al*. [28], and lower exercise capacity than those of OLGIATI *et al*. [10], averaging 36% of their values.

Eight of the 24 patients were not able to perform an arm exercise test. They showed a more severe reduction in RM strength in comparison to patients able to perform effort test.

The original finding of our study is that $\dot{V}O_2$max and HRmax are significantly related to endurance time but not to EDSS. To our knowledge, a relationship between indices of RM function and exercise capacity has not previously been reported in SM patients. Patients with SM suffer from poor physical fitness, as it is a traumatic spinal lesion, a condition partially or totally reversible by adequate physical training. In addition, an abnormally high cost of walking may also contribute to exertional dyspnoea and fatigue [10]. The arm exercise test was related to RM endurance in our patients. It is well-known, that RM function may limit exercise tolerance [13]. CELLI *et al*. [30] showed that unsupported arm

exercise in normal subjects decreased the ventilatory contribution of some of the inspiratory muscles of the rib cage, as they have to partake in nonventilatory functions. They concluded that alterations in ventilatory muscle recruitment during upper arm exercise might be one of the factors decreasing endurance of this type of exercise.

Limitations of the study

The observation that $\dot{V}O_2$max showed a weak correlation with RM endurance, does not demonstrate *per se* that RM dysfunction plays a major role in the reduced exercise capacity. The most likely mechanism of the low $\dot{V}O_2$ is the weakness of the upper limb muscles. Unfortunately, no data regarding the function of these muscles is given, and this is a weak point of the study. Similarly, no measurement of dyspnoea was performed, and it is hard to demonstrate that RM endurance was a significant factor limiting exercise tolerance. The duration of the exercise test was, on average, slightly less than 6 min, that is comparable to the mean endurance time, so that it is unlikely that the patients reached their maximum RM endurance during the exercise test.

Conclusions

In patients with MS, reduction in exercise tolerance was partially associated with reduction in RM function. Nevertheless, there is no firm evidence that RM dysfunction plays a major role in the reduced $\dot{V}O_2$max of patients with multiple sclerosis. The concomitant reduction in $\dot{V}O_2$max and RM endurance may reflect the general disability of the patients.

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