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Ratings of Perceived Exertion During Aerobic Exercise in Multiple Sclerosis

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ABSTRACT. Morrison EH, Cooper DM, White LJ, Larson J, Leu S-Y, Zaldivar F, Ng AV. Ratings of perceived exertion during aerobic exercise in multiple sclerosis. *Arch Phys Med Rehabil* 2008;89:1570-4.

Objective: To compare ratings of perceived exertion (RPEs) during aerobic exercise in people with multiple sclerosis (MS) and control participants.

Design: Prospective experimental study.

Setting: An exercise testing laboratory.

Participants: Sedentary adults (n=12) with mild MS (Expanded Disability Status Scale score ≤ 3) aged 30 to 45 years and sedentary age-matched and sex-matched controls (n=12).

Interventions: All participants underwent a graded aerobic exercise test on a cycle ergometer with breath-by-breath gas measurements and continuous heart rate monitoring.

Main Outcome Measures: After completing the Modified Fatigue Impact Scale, participants rated their effort sense every 30 seconds during exercise using the modified Borg 10-point scale.

Results: The 2 study groups showed similar baseline characteristics except for higher fatigue scores in the MS group. There were no significant differences for any fitness measure, including oxygen cost slope (in $\dot{V}O_2 \cdot \text{min}^{-1} \cdot \text{W}^{-1}$), $\dot{V}O_2$, or work rate during exercise. Neither heart rate nor RPE—measured at 25%, 50%, 75%, and 100% of $\dot{V}O_{2\text{peak}}$ —differed between groups.

Conclusions: Despite greater reported fatigue levels, participants with MS showed similar RPE and physiologic responses to submaximal and maximal exercise compared with controls. In MS, the Borg 10-point scale may help improve evidence-based exercise prescriptions, which otherwise may be limited by fatigue, motor impairment, heat sensitivity, or autonomic dysfunction.

Key Words: Aerobic exercise; Exertion; Fatigue; Multiple sclerosis; Rehabilitation.

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MULTIPLE SCLEROSIS IS an autoimmune demyelinating disease of the central nervous system and a frequent cause of nontraumatic disability. In MS, exercise is known to provide many preventive and therapeutic benefits.¹ Randomized controlled trials have demonstrated that aerobic exercise training can improve fitness and quality of life in MS^{2,3} across a range of disability levels.^{4,5} Like many others with disabling conditions,⁶ people with MS tend to be less physically active than the general population,^{7,8} even when their MS has caused minimal disability.⁹ Rehabilitation and exercise professionals would therefore benefit from additional information for helping people with MS exercise safely and effectively. Past research has not fully clarified why people with MS tend to exercise less, apart from decreased conditioning.⁷ We question whether people with MS may perceive greater exercise effort.

RPEs are practical and cost-effective tools for assessing exercise effort among people with and without disabling conditions.¹⁰ Using RPE data generated during exercise testing, rehabilitation professionals can tailor symptom-specific exercise prescriptions. Yet our collective knowledge base lacks data on how best to use RPE in people with MS. MS often causes signs and symptoms that could alter the sense of exertion, including symptomatic fatigue, the most frequently reported MS symptom.¹¹⁻¹³ This abnormal fatigue likely stems from multiple factors,^{14,15} may be debilitating even early in the disease course, and may unduly increase effort sense during exercise as it does during daily activities. Furthermore, cardiovascular autonomic dysfunction, which has been reported in 25% to 75% of people with MS,^{16,17} could potentially prohibit using heart rate to gauge exertion levels accurately.¹⁸ Finally, central motor impairment during exercise is common in MS¹⁹ and could increase perceived exertion during exercise, as could heat sensitivity.²⁰ Any of these common factors could affect RPE in MS, especially if symptomatic fatigue and effort sense share a common neural substrate, as recent data suggest.²¹

Despite this theoretical rationale for why MS might result in altered RPE during exercise, at least 2 research groups have found that people with mild-to-moderate MS rate their isometric exercise effort similarly to controls when using the modified Borg 10-point RPE scale.^{22,23} Other investigators have studied another Borg scale (the 6–20 version) in aerobic arm-leg ergometry exercise for people with MS²⁰ but not compared with controls. Although MS exercise programs commonly use RPE for exercise prescriptions, to our knowledge no controlled

List of Abbreviations

BMI	body mass index
EDSS	Expanded Disability Status Scale
MAS	Modified Ashworth Scale
MFIS	Modified Fatigue Impact Scale
MS	multiple sclerosis
RPE	rating of perceived exertion
$\dot{V}O_2$	oxygen consumption

study has yet been published that systematically investigates the use of RPE during dynamic or aerobic exercise in MS.

To begin addressing these knowledge gaps, we undertook the present study to determine how the RPE response to aerobic exercise in a group of ambulatory adults with MS would compare with the RPE response of control participants without MS. Our primary objective was to compare psycho-physiologic and physiologic responses to graded endurance or aerobic exercise testing (particularly responses on the Borg 10-point RPE scale) between ambulatory people with mild MS and matched control participants who were equally sedentary. We hypothesized that in the participants with MS, RPE—at any relative work intensity—would exceed RPE of healthy control participants during graded cycling exercise.

METHODS

Participants

We screened a total of 59 potential study participants who responded to recruitment advertisements (on bulletin boards and web sites at our urban university, and in National Multiple Sclerosis Society publications) or received referrals from their MS physicians. We excluded 11 respondents because of MS-related disability or other medical problems. To make fitness levels as equivalent as possible between the study groups, we excluded 5 other candidates (including 4 with MS) because they were too physically active to meet the inclusion criterion of Modified Baecke Questionnaire of Habitual Physical Activity^{24,25} score of 8.5 or less. Nineteen candidates did not enroll for various other reasons, such as work schedules or failure to follow up after the initial telephone screening.

Of the 59 initial candidates, we enrolled a total of 24 sedentary adults (4 men, 20 women) between 30 and 45 years of age. Twelve participants had mild MS as defined by an EDSS²⁶ score of 3 or less, with the EDSS administered by an investigator certified for the Neurostatus e-Test (<http://www.neurostatus.net>). We matched each MS participant by age (2-year difference or less) and sex to 1 of 12 control participants without MS. All completed the Baecke questionnaire and a medical history review to verify fit with the study's inclusion criteria. We also screened the participants' BMI, blood pressure, heart rate, body temperature, and electrocardiogram before they began to exercise.

Participants with MS met additional inclusion criteria, including current adherence to one of the approved disease-modifying therapies for MS. Exclusion criteria for both study groups included pregnancy, morbid obesity as defined by BMI of 40kg/m² or more, substantial cognitive impairment, cardiopulmonary disease or other condition prohibiting safe exercise testing, MS exacerbation within 3 months of enrollment, and an MAS²⁷ score greater than 3. We obtained approval from the University of California, Irvine, Institutional Review Board, and all participants gave written informed consent.

Aerobic Exercise Testing

During a single 90-minute study visit, each participant underwent a standardized, graded exercise test using an Ergometrics 800 cycle ergometer with VMax Spectra metabolic analysis system,^a with breath-by-breath measures of ventilation and gas exchange and monitoring of heart rate, blood pressure, and 12-lead electrocardiogram. All testing occurred between 7:00 AM and 12:00 M in a temperature-controlled laboratory (21°C). Each test began with a 3-minute unloaded warm-up period, followed by a continuous ramp-type increase in workload of 5 to 20W/min to ensure a test lasting 8 to 12 minutes

or until the participant reached a symptom-limited maximum.²⁸ To protect participants' safety, we followed the American College of Sports Medicine's indications for terminating testing if excessive fatigue or any other concerning symptoms occurred.²⁹ We asked all participants afterward to state the sensations that caused them to stop the test. At the same study visit, we collected blood lactate samples immediately before and after exercise from an indwelling catheter placed in the antecubital vein.

Descriptive and Outcome Measures

We obtained each participant's height and mass using standard, calibrated scales and stadiometers, and calculated the BMI. Participants in both study groups underwent whole-body dual-energy x-ray absorptiometry for lean body mass with a Hologic QDR 4500W densitometer.^b During the exercise testing, we determined work rate, heart rate, and ventilatory threshold using the V-slope method.³⁰ We collected breath-by-breath data for $\dot{V}O_2$ and carbon dioxide output. Every 30 seconds during the exercise testing, participants rated their effort sense using the modified 10-point Borg visual analog scale.³¹ From the individual exercise data, we also calculated each participant's oxygen cost slope (in $\dot{V}O_2 \cdot \text{min}^{-1} \cdot \text{W}^{-1}$). Because participants provided an RPE only every 30 seconds, we obtained the corresponding heart rate and relative work level (percentage of $\dot{V}O_{2\text{peak}}$) for each reported RPE. Other outcome measures included the 21-item MFIS (which reflects baseline fatigue over the preceding month),³² which we administered once before exercise and for which we calculated summary scores as well as physical, cognitive, and psychosocial subscale scores. We measured serum lactate with a YSI lactate analyzer^c with a sensitivity of .01mmol/L.

Data Analyses

Using 2-sample *t* tests and (when variables were not normally distributed) Wilcoxon-Mann-Whitney rank-sum tests, we evaluated the differences between the MS and control groups for baseline characteristics, fitness measures (ventilatory threshold, peak work rate, $\dot{V}O_{2\text{peak}}$, oxygen cost slope), RPE, and heart rate at relative work levels, and posttest serum lactate levels. We then applied mixed-model analysis, a statistical method for repeated measurements, to evaluate whether the 2 groups had different patterns of work rate, $\dot{V}O_2$, heart rate, and RPE through the exercise protocol, adjusting for covariates such as sex, weight, and work rate. All statistical results were obtained from SAS,^d and the statistical significance level was set at .05.

RESULTS

Participants

Table 1 summarizes the baseline characteristics of the MS and control participants. All 24 participants completed the study without difficulty. The groups did not differ appreciably on baseline characteristics except for fatigue (MFIS summary scores and physical subscale scores). MS and control participants scored similarly on BMI, Baecke scores, and pretest lactate levels. Among the MS participants, the median EDSS score was 2.75 (range, 0–3). The mean MAS score \pm SD was $.50 \pm .67$ (range, 0–2). Seven (58%) of the MS participants were using interferons for disease-modifying therapy, and 5 (42%) were using glatirimer acetate.

Responses to Aerobic Exercise Testing

We found no significant differences between the MS and control groups for any physiologic or psychophysiological

Table 1: Baseline Characteristics of the Participants With MS and Control Participants

Characteristic	MS Group (n=12)	Control Group (n=12)	P (2-sample t test)
Age (y)	38.3±4.9	37.9±4.9	.84
Height (cm)	161.5±10.1	167.7±9.4	.13
Mass (kg)	68.8±17.2	71.2±19.7	.76
BMI (kg/m ²)	26.3±6.2	25.0±4.8	.54
Lean body mass (kg)	44.4±10.9	47.1±11.8	.58
Body fat percentage (DEXA scan)	33.1±9.6	31.9±7.5	.73
Resting mean arterial blood pressure (mmHg)	91.8±12.3	89.2±12.1	.61
Pretest serum lactate level (mmol/L)	1.81±0.70	1.89±0.49	.74
Baecke score	6.6±1.4	6.5±1.0	.84
MFIS total score	34.0±16.2	18.8±16.9	.035
MFIS physical subscore	17.8±9.2	7.8±7.4	.008
MFIS cognitive subscore	13.3±7.9	9.0±8.2	.20
MFIS psychosocial subscore	2.9±2.3	2.0±1.9	.30

NOTE. Values are means ± SDs.
Abbreviation: DEXA, dual-energy x-ray absorptiometry.

characteristic (table 2), including oxygen cost slope (in $\dot{V}O_2 \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) and the patterns of work rate, RPE, heart rate, and $\dot{V}O_2$ during the exercise protocol. Postexercise lactate increased 6.80 ± 1.85 mmol/L in the MS group and 8.96 ± 3.64 mmol/L in the control group, not a significant difference between the 2 groups. Neither the mean RPE nor the mean heart rate measured at 25%, 50%, 75%, and 100% of $\dot{V}O_{2\text{peak}}$ differed significantly between controls and participants with MS (fig 1). The participants' stated reasons for stopping the testing varied little between the study groups, with 8 of 12 participants with MS and 10 of 12 controls giving leg fatigue as the primary reason. The remainder cited other causes: overall fatigue (2 MS, 1 control), "breathing got hard" (MS), "light-headed" (control), and discomfort with the mouthpiece (MS).

DISCUSSION

To our knowledge, ours is the first study that systematically uses RPE to assess perceived exertion in MS and control participants during incremental exercise testing. We achieved our goal of enrolling study groups comparable for age, sex, body composition, and sedentary levels of physical activity. Contrary to our hypothesis and despite higher baseline fatigue scores in our participants with MS, both groups yielded similar ratings of perceived exertion during graded exercise testing on a cycle ergometer. Our observations suggest that symptomatic fatigue as assessed by the MFIS may not be linked to effort sense during physical exertion, possibly reflecting stimulation of different neural pathways. Because our MS and control groups exhibited similar $\dot{V}O_{2\text{peak}}$, there were no appreciable

Table 2: Comparison of Exercise Testing Data for the MS and Control Participants

Characteristic	MS Group (n=12)	Control Group (n=12)	P (2-sample t test)
$\dot{V}O_{2\text{peak}}$ (L/min)	1.5±0.5	1.8±0.6	.22
$\dot{V}O_{2\text{peak}}$ per kg of TBW (mL·kg ⁻¹ ·min ⁻¹)	22.9±6.2	25.7±5.3	.24
Percentage predicted $\dot{V}O_{2\text{peak}}$ per kg of TBW (mL·kg ⁻¹ ·min ⁻¹)*	66.4±19.3	74.2±16.3	.30
$\dot{V}O_{2\text{peak}}$ per kg of LBM (mL·kg ⁻¹ ·min ⁻¹)	34.7±6.7	38.3±5.2	.16
Ventilatory threshold (L/min)	0.9±0.2	1.0±0.2	.24
Ventilatory threshold as % $\dot{V}O_{2\text{peak}}$ per kg of LBM (mL·kg ⁻¹ ·min ⁻¹)	62.4±15.3	57.3±8.9	.33
Peak work rate (W)	111.6±36.2	135.5±46.4	.17
Maximum heart rate (beats/min)	158.6±12.6	160.7±29.5	.82
Slope, $\dot{V}O_2$, vs work rate (mL·min ⁻¹ ·W ⁻¹)	9.3±1.3	9.1±1.0	.61
Total exercise test duration (s)	540.0±80.0	553.3±88.2	.70
Posttest serum lactate level (mmol/L) [†]	6.80±1.85	8.96±3.64	.09

Characteristic	MS Group (n=12)	Control Group (n=12)	Wilcoxon-Mann-Whitney Rank-Sum Test
RPE at 25% of $\dot{V}O_{2\text{peak}}$	0.25 (0.0–0.5)	0.0 (0.0–1.0)	.87
RPE at 50% of $\dot{V}O_{2\text{peak}}$	1.0 (0.0–3.0)	2.0 (0.0–3.0)	.33
RPE at 75% of $\dot{V}O_{2\text{peak}}$	4.0 (0.5–6.0)	4.0 (2.0–6.0)	.86
RPE at 100% of $\dot{V}O_{2\text{peak}}$	8.5 (4.0–10.0)	7.0 (4.0–9.0)	.19

NOTE. Values are means ± SDs or medians (ranges).

Abbreviations: LBM, lean body mass; TBW, total body weight.

*Predicted $\dot{V}O_{2\text{peak}}$ was calculated for men as $60 - (0.55 \times \text{age})$, and for women as $48 - (0.37 \times \text{age})$.³⁹

[†]We obtained serum samples just before and just after each participant's exercise test from an indwelling catheter placed in the antecubital vein 20 to 30 minutes before the first blood sampling. Lactate showed a significant change from pretest to posttest ($P < .001$) within both study groups, but the change did not differ between the 2 groups.

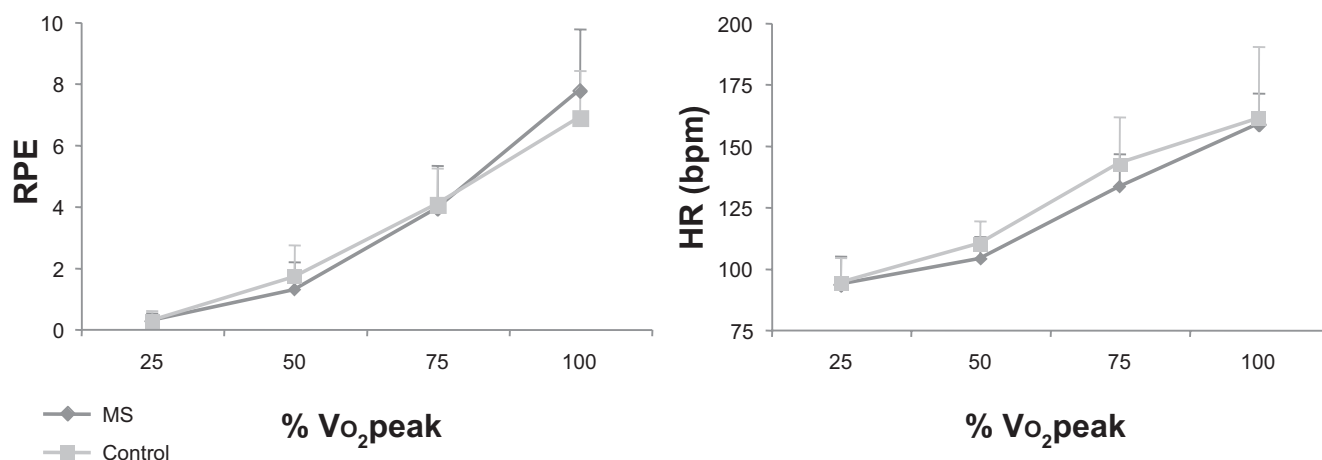


Fig 1. Mean ratings of perceived exertion and heart rate (HR) during an incremental aerobic exercise test, MS, and control groups. Twelve sedentary participants with minimal to mild disability from MS (EDSS score ≤ 3) and 12 sedentary, age-matched and sex-matched control participants rated their perceived exertion on the Borg 10-point visual analog scale every 30 seconds throughout an incremental aerobic exercise test on a cycle ergometer. Two-sample, 2-tailed *t* tests and mixed-model analysis revealed no significant differences between study groups for RPE or heart rate at any relative work load. NOTE. Values are group means \pm SDs.

differences in the absolute work performed that could confound comparisons at relative work intensities. Despite the exercise test's short duration, lactate levels after the testing rose significantly within both study groups, demonstrating that participants did achieve the expected metabolic response to the heavy exercise.

Overall, our results extend those of previous investigations exploring the Borg 10-point scale^{22,33} and 6 to 20 scale²⁰ for isometric exercise testing in MS. For dynamic exercise, Petajan et al² measured mean Vo_2peak levels \pm SE between 24.2 ± 1.4 and $26.0 \pm 1.3 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ for their ambulatory subjects with MS with EDSS score less than 6, using an arm-leg ergometer for graded exercise testing. Although direct comparison with this previous study is not possible because of differences in testing ergometers and EDSS scores, it would appear that our MS group's mean Vo_2peak results of $22.9 \pm 6.2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ during leg-only cycling are at least somewhat comparable. This finding suggests these studies are representative of the ambulatory MS population. Cohen et al³⁴ likewise reported similar mean peak RPE and Vo_2peak among 5 subjects with mild MS (mean EDSS score, 1.7) and 11 controls who completed graded aerobic exercise testing on a cycle ergometer. Our control and MS groups demonstrated oxygen costs (mean $\text{Vo}_2\text{peak} \pm$ SE, $9.1 \pm 1.0 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ and $-9.3 \pm 1.3 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) resembling those that Wasserman and Whipp³⁵ reported for healthy but sedentary volunteers ($10.1 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$), suggesting similar energy economy.

In cardiac rehabilitation, researchers have validated Borg RPE ratings as a means of providing appropriate exercise prescriptions when patients cannot use heart rate to estimate their exertion.³⁶⁻³⁸ Our results extend the use of RPE to people with mild MS who want to gain the benefits of aerobic conditioning. RPE in fact might indicate effort more accurately than a prescribed heart rate could for any condition in which baroreflexes would tend to slow the pulse, such as aquatic or recumbent exercise (ie, cycling in a recumbent or semirecumbent position).

Study Limitations

Readers should note limitations to our study design. Ours was a preliminary study in an urban university setting that

included participants with MS with only mild disability, limiting its generalizability to other groups. We recruited a sedentary control sample (with percentage of predicted Vo_2peak means of 66.4% in the MS group and 74.2% in the control group), providing the advantage of well-matched study groups but conferring the potential drawback that our controls may not have closely resembled the general young adult population. We did not attempt to screen eligible participants with MS for heat sensitivity, the presence or absence of which may have affected the study's results.

CONCLUSIONS

Our data add to the evidence-supported knowledge base about exercise in MS. We hope this study will assist MS and rehabilitation professionals with exercise testing and prescription by highlighting a simple means for people with MS to calibrate their effort sense to physiologic parameters for appropriate exercise intensity and duration. Despite reporting greater baseline fatigue, our participants with MS showed no significant differences from controls in exercise RPE, suggesting that the overall perceptions of symptomatic fatigue and effort sense might be modulated by different neural structures or pathways. It remains to be seen how RPE interacts with aerobic exercise among people with a wider range of MS disability.

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References

- White LJ, McCoy SC, Castellano V, Ferguson MA, Hou W, Dressendorfer RH. Effect of resistance training on risk of coronary artery disease in women with multiple sclerosis. *Scand J Clin Lab Invest* 2006;66:351-5.
- Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* 1996;39:432-41.
- Romberg A, Virtanen A, Ruutiainen J, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. *Neurology* 2004;63:2034-8.

4. Solari A, Filippini G, Gasco P, et al. Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. *Neurology* 1999;52:57-62.
5. Freeman JA, Langdon DW, Hobart JC, Thompson AJ. The impact of inpatient rehabilitation on progressive multiple sclerosis. *Ann Neurol* 1997;42:236-44.
6. Cardinal BJ, Kosma M, McCubbin JA. Factors influencing the exercise behavior of adults with physical disabilities. *Med Sci Sports Exerc* 2004;36:868-75.
7. Ng AV, Kent-Braun JA. Quantitation of lower physical activity in persons with multiple sclerosis. *Med Sci Sports Exerc* 1997;29:517-23.
8. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. *Mult Scler* 2005;11:459-63.
9. Tantucci C, Massucci M, Piperno R, Grassi V, Sorbini CA. Energy cost of exercise in multiple sclerosis patients with low degree of disability. *Mult Scler* 1996;2:161-7.
10. Dawes HN, Barker KL, Cockburn J, Roach N, Scott O, Wade D. Borg's rating of perceived exertion scales: do the verbal anchors mean the same for different clinical groups? *Arch Phys Med Rehabil* 2005;86:912-6.
11. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* 1984;65:135-8.
12. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* 1994;21:9-14.
13. Goodin DS. Survey of multiple sclerosis in northern California. Northern California MS Study Group. *Mult Scler* 1999;5:78-88.
14. Iriarte J, Subira ML, Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Mult Scler* 2000;6:124-30.
15. Tartaglia MC, Narayanan S, Francis SJ, et al. The relationship between diffuse axonal damage and fatigue in multiple sclerosis. *Arch Neurol* 2004;61:201-7.
16. Anema JR, Heijenbrok MW, Faes TJ, Heimans JJ, Lanting P, Polman CH. Cardiovascular autonomic function in multiple sclerosis. *J Neurol Sci* 1991;104:129-34.
17. Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. *Acta Neurol Scand* 2000;101:85-8.
18. Senaratne MP, Carroll D, Warren KG, Kappagoda T. Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1984;47:947-52.
19. Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. *Muscle Nerve* 2004;29:843-52.
20. White AT, Wilson TE, Davis SL, Petajan JH. Effect of precooling on physical performance in multiple sclerosis. *Mult Scler* 2000;6:176-80.
21. Thickbroom GW, Sacco P, Kermode AG, et al. Central motor drive and perception of effort during fatigue in multiple sclerosis. *J Neurol* 2006;253:1048-53.
22. Ng AV, Dao HT, Miller RG, Gelinas DF, Kent-Braun JA. Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. *J Appl Physiol* 2000;88:871-80.
23. Pepin EB, Spencer MK, Hicks RW, Jackson CG, Tran ZV. Reliability of a handgrip test for evaluating heart rate and pressor responses in multiple sclerosis. *Med Sci Sports Exerc* 1998;30:1296-8.
24. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36:936-42.
25. Pols MA, Peeters PH, Bueno-De-Mesquita HB, et al. Validity and repeatability of a modified Baecke questionnaire on physical activity. *Int J Epidemiol* 1995;24:381-8.
26. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurol* 1983;33:1444-52.
27. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987;67:206-7.
28. Beck KC, Weisman IM. Methods for cardiopulmonary exercise testing. In: Weisman IM, Zeballos RJ, editors. *Progress in respiratory research: clinical exercise testing*. Basel: Karger; 2002. p 43-59.
29. Whaley MH, editor. *ACSM's guidelines for exercise testing and prescription*. American College of Sports Medicine. 7th ed. Baltimore: Lippincott Williams & Wilkins; 2006.
30. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of exercise testing and interpretation*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.
31. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc* 1983;15:523-8.
32. Kos D, Kerckhofs E, Carrea I, Verza R, Ramos M, Jansa J. Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Mult Scler* 2005;11:76-80.
33. Pepin EB, Hicks RW, Spencer MK, Tran ZV, Jackson CG. Pressor response to isometric exercise in patients with multiple sclerosis. *Med Sci Sports Exerc* 1996;28:656-60.
34. Cohen J, Hossack K, Franklin G. Multiple sclerosis patients with fatigue: relationship among temperature regulation, autonomic dysfunction and exercise capacity. *J Neurol Rehabil* 1989;3:193-8.
35. Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis* 1975;112:219-49.
36. Dunbar CC, Glickman-Weiss EL, Bursztyl DA, Kurtich M, Quiroz A, Conley P. A submaximal treadmill test for developing target ratings of perceived exertion for outpatient cardiac rehabilitation. *Percept Mot Skills* 1998;87:755-9.
37. Dunbar CC, Glickman-Weiss EL, Edwards WW, Conley P, Quiroz A. Three-point method of prescribing exercise with ratings of perceived exertion is valid for cardiac patients. *Percept Mot Skills* 1996;83:384-6.
38. Shephard RJ, Kavanagh T, Mertens DJ, Yacoub M. The place of perceived exertion ratings in exercise prescription for cardiac transplant patients before and after training. *Br J Sports Med* 1996;30:116-21.
39. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis* 1976;113:587-600.

Suppliers

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