ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2015;■:■■■-■■■

REVIEW ARTICLE

Feasibility and Safety of Cardiopulmonary Exercise Testing in Multiple Sclerosis: A Systematic Review

Lizanne Eva van den Akker, MSc,[a,b] Martin Heine, MSc,[c] Nikki van der Veldt, MSc,[a,d] Joost Dekker, PhD,[a,b] Vincent de Groot, MD, PhD,[a,b] Heleen Beckerman, PhD, PT[a,b]

From the [a]Department of Rehabilitation Medicine, Vrije Universiteit University Medical Center, Amsterdam; [b]EMGO Institute for Health and Care Research, Vrije Universiteit University Medical Center, Amsterdam; [c]Rudolf Magnus Institute of Neuroscience and Center of Excellence for Rehabilitation Medicine, University Medical Center Utrecht and Rehabilitation Center De Hoogstraat, Utrecht; and [d]Faculty of Medicine, Vrije Universiteit University Medical Center, Amsterdam, The Netherlands.

Abstract

Objective: To investigate the feasibility and safety of cardiopulmonary exercise testing (CPET) in patients with multiple sclerosis (MS).

Data Sources: PubMed, EMBASE, CINAHL, SPORTDiscus, PsycINFO, ERIC, and the Psychology and Behavioral Sciences Collection were searched up to October 2014. References from retrieved articles were examined to identify additional relevant studies.

Study Selection: Inclusion of original studies was on the basis of performance of maximal CPET, description of the protocol, and participants with definite MS aged ≥18 years. No language restrictions were applied.

Data Extraction: The quality of CPET reporting in included studies was scored according to a structured checklist considering 10 feasibility (eg, test abnormalities) and 12 safety quality criteria (eg, adverse events). Structured data extraction was performed for these feasibility and safety features of CPET.

Data Synthesis: Forty-six studies were included, comprising 1483 patients with MS, with a mean age ± SD of 42.0±5.8 years and a median Expanded Disability Status Scale (EDSS) score of 2.8 (first quartile = 2.1; third quartile = 3.9; range of average EDSS scores, .75−5.8). Quality of reporting on CPET varied from 3 to 13 out of a possible 22 quality points. The percentage of test abnormalities (feasibility) was 10.0%, primarily because of an inability to maintain pedaling at a specific resistance. The percentage of adverse events (safety) was 2.1%. All adverse events were temporary.

Conclusions: Based on the available data, we conclude that CPET is feasible provided that the CPET modality is tailored to the physical abilities of the patient. Furthermore, CPET is safe when recommended precautions and safety measures are implemented. However, future optimization of CPET will require protocolized testing and the implementation of standard reporting procedures.

Archives of Physical Medicine and Rehabilitation 2015;■:■■■-■■■

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system that results in damage to myelin and axons. The estimated prevalence of MS in Europe is 80 cases per 10,000 people, and the average age of onset ranges from 25 to 32 years, with women twice as likely to be affected as men.[1] MS is an unpredictable disease, with symptoms that can develop acutely, remain stable for a certain period, and then recede.[2] MS symptoms include muscle weakness, poor balance, spasms, pain and fatigue, cognitive impairment, and depression.[2] These impairments are common and often explain the reduction in physical activity and decrease in physical fitness and deconditioning. In general, patients with MS tend to be less physically active than healthy persons.[3,4] Physical inactivity is now a pandemic health problem, particularly in people with disabilities, which recently led to a worldwide campaign to promote physical activity.[5]

General attitudes toward physical activity in patients with MS have changed considerably over time.[6] In 1889, Uhthoff[7] advised patients with MS to avoid physical activity on the grounds that symptoms can be exacerbated by elevated body temperatures. This led health care specialists to advise patients with MS to avoid physical activity. By contrast, modern views are based on the well-established positive effects of physical activity and aerobic exercise in patients with MS in terms of physical fitness,

Supported by the Fonds NutsOhra (grant no. ZonMW 89000005). This article is performed on behalf of the Treating Fatigue in Multiple Sclerosis, Aerobic Training, Cognitive Behavioral Therapy and Energy Management study.

Disclosures: none.

0003-9993/15/$36 - see front matter © 2015 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2015.04.021

comorbidities, and quality of life.[8-11] Unresolved questions mainly involve determining the most beneficial type, intensity, and duration of exercise interventions.[8,12] Prescribing the optimal intensity of aerobic training requires objective measurement of each patient's physical fitness.

The American College of Sports Medicine defines physical fitness as a combination of cardiovascular fitness, muscular strength, muscular endurance, body composition, and flexibility.[13] Cardiovascular fitness can be determined by measurement of maximal oxygen uptake ($\dot{V}O_2max$), which is defined as the ability of the cardiopulmonary system to deliver oxygen to skeletal muscles and the efficiency of muscles in using oxygen.[14,15] In clinical practice, the measurement of cardiopulmonary fitness in patients with MS is aimed at (1) evaluating aerobic capacity, (2) defining an appropriate exercise intensity, and (3) monitoring the effects of exercise training and other interventions on physical fitness.

In healthy participants, the criterion standard for determining cardiopulmonary fitness is the cardiopulmonary exercise test.[16] The cardiopulmonary exercise test is a graded exercise test until voluntary exhaustion, and it is usually conducted on a bicycle ergometer or treadmill. The American Thoracic Society/American College of Chest Physicians (ATS/ACCP) described cardiopulmonary exercise testing (CPET) as "an assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function."[17(p212)]

The so-called primary criterion for attainment of maximum aerobic capacity ($\dot{V}O_2max$) in adults is an oxygen consumption ($\dot{V}O_2$) plateau, despite a further increase in work rate.[18,19] Since this plateau will not be reached often in practice, the ATS/ACCP recommends that $\dot{V}O_2$ should be derived from the highest $\dot{V}O_2$ value obtained during an incremental exercise test.[17] The highest attainable $\dot{V}O_2$ is referred to as peak oxygen uptake (VO_2peak). In practice, only about a third of healthy subjects will reach a $\dot{V}O_2$ plateau under maximal effort because most participants cannot endure the discomfort long enough to sustain a plateau in $\dot{V}O_2$.[19] Because of various forms of discomfort such as shortness of breath, leg or chest pain, these individuals are said to reach symptom-limited exhaustion.[19] Although VO_2peak will not satisfy the definition of $\dot{V}O_2max$ in such cases, $\dot{V}O_2max$ and VO_2peak are often used interchangeably in the current literature.[14,16] We therefore chose to use the term $\dot{V}O_2max$ in this review to indicate both $\dot{V}O_2max$ and VO_2peak.

Although the role of physical fitness in the clinical management of MS now receives greater attention and the use of CPET is increasing, during a recent multicenter research program on MS fatigue we encountered widely differing responses from medical ethics committees, with some committees stipulating strict standard operating procedures for CPET. However, a brief literature search revealed that there is no solid evidence on appropriate procedures for CPET in patients with MS, and there is also no data available on safety. Comparable comprehensive reviews have been recently published on CPET in cancer rehabilitation.[20,21]

The goal of the present systematic review was to synthesize the available evidence regarding the feasibility and safety of CPET in determining the aerobic fitness of patients with MS. The adherence of studies to international CPET guidelines was also assessed.[17]

Features of feasibility that should be considered in patients with MS include which patients to select with respect to, for example, age, severity of disease or comorbidities, and determining how CPET should be performed (ie, the most appropriate CPET modalities and protocols). Moreover, the occurrence of test abnormalities has to be considered. Safety features that should be considered include preparation for performance of CPET and of the patient, the safety measures required during CPET, and when to end CPET. Furthermore, disease-associated or CPET-associated adverse events should be registered.

List of abbreviations:

ATS/ACCP	**American Thoracic Society/American College of Chest Physicians**
CPET	**cardiopulmonary exercise testing**
ECG	**electrocardiogram**
EDSS	**Expanded Disability Status Scale**
MS	**multiple sclerosis**
$\dot{V}O_2$	**oxygen consumption**
$\dot{V}O_2max$	**maximal oxygen uptake**
VO_2peak	**peak oxygen uptake**

Methods

Review methods and reporting were in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The database-specific search strategies, data extraction, data synthesis, and analysis were performed according to a prespecified protocol (available on request from the corresponding author).

Literature search

Conclusions on the feasibility and safety of CPET were based on articles published up to October 2014. The electronic databases PubMed (MEDLINE), EMBASE, CINAHL, SPORTDiscus, PsycINFO, ERIC, and Psychology and Behavioral Sciences Collection were searched using the following keywords: cardiopulmonary exercise test, exercise test, $\dot{V}O_2max$, VO_2peak, oxygen uptake, fitness, and physical exertion. These keywords were combined with multiple sclerosis and MS. There were no language restrictions or restrictions on the design of the studies.

Two reviewers (L.A., H.B.) implemented the search strategy independently. Selection was based first on title and abstract, followed by screening of the full-text articles for inclusion. References from retrieved articles were then examined to identify additional studies that met the inclusion criteria.

Study selection

Articles were included if they met the following inclusion criteria: (1) they were original studies; (2) participants were aged $\geq$18 years and had received a diagnosis of definite MS; (3) maximal CPET was performed; and (4) the CPET protocol was reported. Maximal CPET was defined as a test to determine aerobic capacity by means of a graded exercise protocol until voluntary exhaustion. A reported CPET protocol was considered acceptable when it included a description of the manner in which the work rate was applied: (1) continuous progressive; (2) multistage progressive; (3) or discontinuous multistage (with rest between stages).

Data extraction

All articles were systematically scrutinized for quality—defined as reported adherence to aspects of CPET feasibility and safety as