Clinical Biomechanics 30 (2015) 159–165

Contents lists available at ScienceDirect

Clinical Biomechanics

journal homepage: www.elsevier.com/locate/clinbiomech

Glucose uptake heterogeneity of the leg muscles is similar between patients with multiple sclerosis and healthy controls during walking

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ARTICLE INFO

Article history:
Received 13 October 2014
Accepted 9 December 2014

Keywords:
Positron emission tomography
Exercise
[^{18}F]-Fluorodeoxyglucose
Computed tomography
Clinical disability
Muscle fiber activity

ABSTRACT

Background: Difficulties in ambulation are one of the main problems reported by patients with multiple sclerosis. A previous study by our research group showed increased recruitment of muscle groups during walking, but the influence of skeletal muscle properties, such as muscle fiber activity, has not been fully elucidated. The purpose of this investigation was to use the novel method of calculating glucose uptake heterogeneity in the leg muscles of patients with multiple sclerosis and compare these results to healthy controls.
Methods: Eight patients with multiple sclerosis (4 men) and 8 healthy controls (4 men) performed 15 min of treadmill walking at a comfortable self-selected speed following muscle strength tests. Participants were injected with ≈ 8 mCi of [^{18}F]-fluorodeoxyglucose during walking after which positron emission tomography/computed tomography imaging was performed.
Findings: No differences in muscle strength were detected between multiple sclerosis and control groups ($P > 0.27$). Within the multiple sclerosis, group differences in muscle volume existed between the stronger and weaker legs in the vastus lateralis, semitendinosus, and semimembranosus ($P < 0.03$). Glucose uptake heterogeneity between the groups was not different for any muscle group or individual muscle of the legs ($P > 0.16$, $P \geq 0.05$).
Interpretations: Patients with multiple sclerosis and healthy controls showed similar muscle fiber activity during walking. Interpretations of these results, with respect to our previous study, suggest that walking difficulties in patients with multiple sclerosis may be more associated with altered central nervous system motor patterns rather than alterations in skeletal muscle properties.

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1. Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults (Fox et al., 2006). Common symptoms include difficulties walking, muscle weakness, and increased levels of fatigue (Flachenecker et al., 2003; Sandroff et al., 2012; White and Dressendorfer, 2004). Previous studies (Garner and Widrick, 2003; Kent-Braun et al., 1997; Ng et al., 2004) have shown alterations in skeletal muscle properties which have been associated with declines in motor task performance and/or fatigue. These changes include alterations in muscle fiber types (Kent-Braun et al., 1997), reduced muscle relaxation time (Ng et al., 2004), and reduction in the total number of fibers (Garner and Widrick, 2003). Along with the changes in skeletal muscles, alterations in the central activation of these muscles have also been reported (Kent-Braun et al., 1997; Kindred et al., 2014; Ng et al., 2004).

Electromyography (EMG) is the traditional technique used to measure muscle activity. Intramuscular recordings and multi electrode arrays can also provide information on motor unit activity, but only for small portions of superficial muscles. Positron emission tomography (PET) with the glucose analogue [^{18}F]-fluorodeoxyglucose (FDG) has been used to measure activity of whole muscles (Pappas et al., 2001), including deep muscles not accessible by EMG. [^{18}F]-FDG uptake reveals the utilization of ordinary glucose, a major energy source for the human body. Therefore, PET with [^{18}F]-FDG can identify inefficient muscle activation strategies which may play an important role in impaired walking performance and greater fatigability in patients with MS (Laaksonen et al., 2013; Pappas et al., 2001; Rudroff et al., 2013). PET/[^{18}F]-FDG can provide insight into muscle fiber (motor unit) activity by examining the spatial distribution of [^{18}F]-FDG within a muscle (Heinonen et al., 2012; Rudroff et al., 2014a). This process uses the coefficient of variation of [^{18}F]-FDG uptake to estimate glucose uptake heterogeneity (GUh). As more motor units and in turn muscles fibers are recruited, GUh decreases (Heinonen et al., 2012) due to the increased proportion of fibers activated within a muscle.

This technique has been previously used in young and old healthy adults (Heinonen et al., 2012; Rudroff et al., 2014a). Heinonen et al. (2012) showed that as exercise intensity increased GUh decreased

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http://dx.doi.org/10.1016/j.clinbiomech.2014.12.005
0268-0033/Published by Elsevier Ltd.

within the quadriceps femoris in young adults, reflecting the recruitment of more motor units to complete higher intensity tasks. In a study of healthy older adults, Rudroff et al. (2014a) found that increases in GUh were consistent with motor unit remodeling that occurs with aging. Their results showed that older adults had fewer motor units which were distributed less equally throughout muscle tissue and that older men used different muscle activation strategies to perform the same task as young men. Currently, there are no reports of GUh within any neurological/neuromuscular disease populations. Utilizing this technique in these clinical populations may provide new insights into the activation and recruitment of skeletal muscle during functional tasks.

The reduction of muscle fibers (Garner and Widrick, 2003) and the loss of lower motor neurons (Vogt et al., 2009) contribute to the reduced number of motor units within a muscle in patients with MS. Fewer motor units would lead to a reduced ability to activate the working muscle homogenously during contractions and could be a contributing factor to motor deficits and disability in patients with MS. The purpose of this study was to compare GUh in leg muscles of patients with MS and healthy controls during treadmill walking. We hypothesized that patients with MS would show greater GUh in skeletal muscles involved in ambulation compared to healthy controls reflecting alterations in muscle fiber activation and that GUh would be associated with levels of disability.

2. Methods

2.1. Participants

Eight (4 men) mildly disabled patients with the relapsing remitting MS and 8 sex matched controls were recruited from the Denver Colorado area via advertisements through the Rocky Mountain MS Center and University of Colorado–Anschutz Medical Campus study announcement newsletter. All participants signed informed consent approved by the Colorado Multiple Institutional Review Board and were in accordance with the Declaration of Helsinki. Participants were initially screened by phone interview. Requirements to participate in the study for patients with MS were as follows: being 18 to 55 years of age, confirmed diagnosis of MS, able to walk 15 min without assistance, score of <2 for the legs on the Modified Ashworth spasticity scale (MASS) (indicating no greater than minimal level of spasticity), and have had no changes in disease progression in the last 3 months. Main exclusion criteria for patients with MS included relapse within the last 3 months, history of seizures, having an unrelated condition that would exacerbate fatigue, and any medical diagnosis with contraindications to exercise participation. Eight healthy participants without neurological, muscular or skeletal disease were recruited for the control group.

2.2. Experimental protocol

Participants arrived at the Colorado Translational Research Imaging Center during the morning hours following an 8 h fast, and patients with MS were assessed for disability levels utilizing the Patient Determined Disease Steps (PDDS). The PDDS has been validated and shows a high correlation to the Expanded Disability Status Scale (EDSS) (Hohol et al., 1995, 1999; Kobelt et al., 2006; Learmonth et al., 2013; Marrie and Goldman, 2007). Leg spasticity was graded using the MASS. Measurements for height, weight, comfortable walking speed, and muscle strength preceded 15 min of treadmill walking. After completion of treadmill walking, participants immediately underwent PET/computed tomography (CT) imaging. Fig. 1 is a visual representation of the experimental timeline.

2.3. MVC force

Before the walking test, each subject performed an isometric maximal voluntary contraction (MVC) with the knee extensor and knee flexor muscles of the left and right leg. MVC forces were measured with the knee and hip at 90° of flexion. The MVC task comprised a 3 s increase in force from zero to maximum with the maximal force held for ~3 s, and subjects were verbally encouraged to achieve maximal force. Subjects rested for 60 to 90 s between trials. When the peak forces achieved in two of the three trials differed by >5%, additional MVCs were performed until this criterion was met. The greatest force achieved by each subject was taken as the MVC force. Lower-leg length was measured from the head of the fibula to the midpoint of the lateral malleolus. Knee extensor and flexor torque was calculated in newton meters by multiplying the recorded force in newtons by measured lower-leg length in meters. To designate stronger and weaker legs for each group, the torques of the knee extensors and flexors were added together. The higher torque value between the legs determined the stronger leg.

2.4. Walking protocol

Following the MVC testing, participants' plasma glucose levels were tested via finger stick. This ensured that the measurement of glucose uptake began from comparable baseline conditions and that participants did not have impaired glucose regulation. A 22-gauge i.v. catheter was placed into an antecubital vein in the subject's right arm for injection of [^{18}F]-FDG. Subjects then walked on a treadmill for 15 min at a comfortable self-selected pace. The self-selected pace was previously determined by measuring the time each participant took to walk down an 18 m hallway. Three trials were performed, with the average of the two closest times being set as the initial treadmill speed. Two minutes after the start of the treadmill walking test, ≈8 mCi of [^{18}F]-FDG in 10 ml of saline was infused into the vein via the inserted catheter. Once walking began, any adjustments to speed were made within the first 2 min. Immediately after the conclusion of treadmill walking, the catheter was removed and subjects were guided into the PET/CT camera for whole-body imaging utilizing a standard testing protocol used in the Colorado Translational Research Imaging Center.

2.5. PET/CT imaging and analysis

Imaging was performed with a Philips Hybrid Gemini TF 64 scanner (Philips Healthcare, Cleveland, OH, USA). CT imaging was performed first and immediately followed by PET imaging with the subject's body position secured to maintain co-registration.

Regions of interest (ROI) were drawn in the transverse plane by two investigators, confirmed in both sagittal and frontal planes, for 17 leg muscles after identification on each CT image data set using Analyze 11.0 (Analyze Direct, Rochester, MN, USA). Linear regression analysis

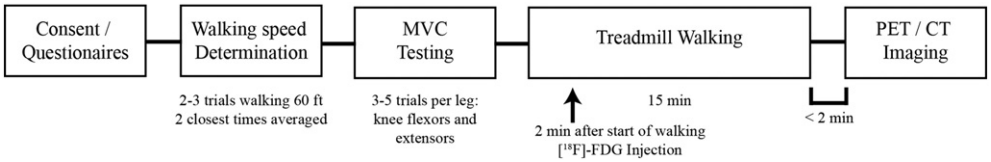

Fig. 1. A visual representation of the experimental procedures timeline.