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Characterizations of reflex and nonreflex changes in spastic multiple sclerosis

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HIGHLIGHTS

- Simultaneous characterization of reflex and nonreflex changes in multiple sclerosis.
- Viscosity and tonic reflex gain were lower with MS.
- Phasic reflex gain and stiffness were higher with MS.

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ABSTRACT

Background: Spasticity, an increased resistance of a limb to movement, is associated with functional limitations and a major source of disability in neurological disorders, including multiple sclerosis (MS) and stroke. Despite the clinical significance of spasticity in brain and spinal cord injuries, it is often not clear whether the spasticity is due to reflex or non-reflex changes.
New method: Reflex and nonreflex properties of the human knee joint were studied in eight MS patients with spasticity and ten healthy subjects. A digitally controlled joint driving device was used to apply small-amplitude, and band-limited white-noise perturbations to the knee to manifest the reflex and nonreflex properties. The subjects were asked to maintain a steady level of background muscle torque during the perturbation. A nonlinear delay differential equation model was used to characterize the reflex and intrinsic properties of the knee in terms of phasic stretch reflex gain, tonic stretch reflex gain, joint elastic stiffness, and coefficient of viscosity.
Results: It was found that joint coefficient of viscosity and tonic stretch reflex gain of the spastic MS patients were significantly lower than those of normal controls. On the other hand, spastic MS patients showed higher phasic stretch reflex gains than normal controls and a trend of increased joint stiffness.
Conclusions: Simultaneous characterizations of changes in tonic and phasic reflexes and nonreflex changes in joint elastic stiffness and viscosity in neurological disorders may help us gain insight into mechanisms underlying spasticity and develop impairment-specific treatment.

1. Introduction

Spasticity, an increased resistance of a limb to externally imposed movement, is associated with functional limitations and a major source of disability in many neurological disorders, including multiple sclerosis (MS), stroke, and traumatic spinal cord injury (Kim and Park, 2011; Sunnerhagen et al., 2013). Despite the clinical significance of spasticity in brain and spinal cord injuries, it is often not clear whether the spastic hypertonia is due to reflex or non-reflex changes in the neuromuscular system (Rymer and Katz, 1994). The reflex changes include phasic and tonic reflex components, and the nonreflex biomechanical changes have the dynamic component of viscosity (dashpot property defined as the ratio of the change of joint torque over that of joint velocity) and static

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component of elastic stiffness (spring property defined as the ratio of the change of joint torque over the change of the joint position).

While several investigators assert that the increased resistance is due to hyperactive reflexes (Gottlieb et al., 1978; Mirbagheri et al., 2001; Rack et al., 1984), others believe that muscle hypertonia is independent of hyperactive reflex and mechanical properties of the muscles involved like muscle fiber contracture are responsible for the increased muscle tone in spasticity (Dietz and Berger, 1983; O'Dwyer and Ada, 1996; O'Dwyer et al., 1996). Lee et al. reported that for voluntarily activated muscles of spastic hemiparetic patients, stretch reflex gain of spastic and contralateral limbs is not significantly different (Lee et al., 1987). Sinkjær et al. reported spastic muscles in MS patients have an increased non-reflex stiffness but that reflex-mediated stiffness during sustained voluntary contraction is not significantly different from normal subjects (Sinkjær and Magnussen, 1994; Sinkjær et al., 1993, 1996). These authors pointed out that increased total joint stiffness can not be directly interpreted as evidence of hyperactive reflex, since matched joint position and muscle force and separation of reflex and non-reflex contribution is required (Sinkjær et al., 1993). The various reflex and nonreflex components may contribute to the increased resistance in passive movement of spastic limbs simultaneously in multiple sclerosis (Chung et al., 2008). Hence evaluating spastic mechanisms purely through the use of clinical measures and/or reflex excitability such as modified Ashworth scale and deep tendon reflex scale cannot suffice in spasticity evaluation of MS. There is a need for methodology and tools to simultaneously quantify the various reflex and nonreflex contributions.

The objectives of this study were to identify simultaneously reflex and intrinsic changes in the spastic knee muscles of MS patients. A model based on nonlinear delay differential equation was used to quantify the static and dynamic stretch reflex gains, joint stiffness, viscosity, and limb inertia (Zhang and Rymer, 1997). Quantification of these reflex and intrinsic properties helps us gain insights into the mechanisms underlying spasticity and evaluate the pathological changes and assess treatment outcome.

2. Materials and methods

2.1. Subject selection

Ten healthy subjects with no prior history of muscular injury and neurological disorders and eight chronic MS patients with spasticity at the knee participated in the study (Table 1). All the subjects gave informed consent before participating in the study, which was approved by the Institutional Review Board. The Ashworth scale (0–4) was evaluated for each of the patients. The passive limb movement was done throughout the range of motion, and about three trials were conducted before the Ashworth scale was determined (Bates, 1991; Meythaler et al., 1996). Clinical tendon reflex scale (0–4) was evaluated by tapping the patellar tendon at its most sensitive spot (Scale 0 mans no response, 1 low normal, 2 average normal, 3 brisker the average, possibly indicative of disease, and 4 very brisk, hyperactive, associated with clonus) (Bates, 1991; Meythaler et al., 1996; Zhang et al., 2000). Muscle strength was measured in knee flexion and extension (Table 1).

2.2. Experimental setup

With the subject seated upright, a general-purpose joint driving device was used to perturb the knee joint in precisely controlled patterns to excite the reflex and intrinsic properties of the knee neuromuscular system under various conditions (Fig. 1). The seat could be moved in the horizontal plane along two levels of tracks perpendicular to each other. It could also be rotated to an appropriate orientation and raised to different heights so that knee flexion–extension axis was aligned with the motor shaft. Once the knee was moved to a desired position, the seat was locked in all the four degrees of freedom to form a solid base. A short leg cast (covering from distal leg to proximal foot with the ankle at 15° plantar flexion) was made with fiberglass tape and fixed to one end of an aluminum beam located on the lateral side of the leg through two adjustable half-rings. The other end of the beam was mounted onto the motor shaft through a six-axis force sensor (JR3 Inc., Woodland, CA). The relative position between the cast and beam was adjusted in the directions of medio-lateral, anterior–posterior, proximal–distal, and axial rotation directions of the leg so that the leg was aligned with the beam and no excessive compressive load was exerted onto the knee joint due to the mounting. The trans-epicondyle line was aligned with the motor shaft and a custom pointer was used to align the medial epicondyle with the motor shaft (see insert in Fig. 1). The knee and hip were flexed at 30° and 85°, respectively.

2.3. Joint perturbations

The joint driving device was driven directly by a powerful servomotor (Kollmorgan Goldline B806) with a peak torque of 360 N m. A digital controller using Texas Instruments' TMS320 digital signal processor (DSP) was used to control the servomotor and checked the joint position and torque signals at 2 kHz and would shutdown the system if they were out of pre-specified ranges. A small-amplitude band-limited white-noise sequence with a standard deviation of 5° and bandwidth of about 10 Hz was used as the position command by the controller to perturb the knee joint and manifest both reflex and intrinsic mechanical properties. The perturbation trajectory was determined by the powerful motor whether the subject strenuously contracted his/her lower limb muscles or not.

2.4. Protocol

Knee flexion angle $\theta(t)$ and moment $T(t)$ were low-pass filtered with 8th-order Butterworth filters at 230 Hz cutoff frequency and sampled at 500 Hz. At first, all the signals were recorded at quiescent level while the subject remains relaxed. Next, isometric maximum voluntary contraction (MVC) in the directions of flexion and extension were measured and the flexion MVC and extension MVC measurements were repeated twice.

To excite the reflex and intrinsic properties involved, the knee joint was perturbed with small-amplitude and band-limited white-noise perturbation. The subject was asked to either relax or maintain a steady background muscle torque by matching a target torque. The target background muscle torque was specified by the experimenter for each trial, and target torque matching error was calculated and displayed on the computer monitor screen in real-time. The subject was instructed to simply keep the average level of the *error* at zero, whatever the target torque level was. Generally, two trials were done under the relaxed condition (subject was asked to relax during the perturbation), two torque levels for background knee flexor contraction, and two torque levels for background knee extensor contraction. Background flexion and extension muscle torques were generated alternately in a typical sequence of 0%, 15%, −15%, 30%, −30% and 0% of flexor MVC torque (the subjects actually generated background extensor muscle torque during a negative percentage of flexor MVC effort). Emphasis was placed on generating a steady level of background muscle contraction and the exact level was not important. If the subjects generated a background torque level lower than the specified torque level, they were asked to just keep the torque steady at