Quantifying Spasticity in Spinal Rats

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Abstract

The goal of this project was to develop a sensitive method for quantifying spasticity in a rat model of spinal cord injury (SCI). The tails of adult rats were chronically paralyzed due to a complete spinal transaction at S2/S3. Two days to 3 weeks following spinalization, the tails developed marked spasticity and exhibited hyperreflexia, hypertonus, clonus and spasms. To quantify the level of spasticity, a feedback-controlled torque motor was used to induce controlled displacements of the tail and the tail's resistance to stretch was measured using a force transducer. Elastic and viscous stiffness were calculated and mechanical impedance was determined. Mechanical impedance was obtained under multiple experimental conditions (e.g., awake animals exhibiting hypertonus, baclofen-induced suppression of tonus, and anesthesia) and was found to be a sensitive, reliable, and repeatable measure of muscle tone. This quantification technique is easy to apply and provides a dependable method for assessing spasticity. It also allows for objective evaluation of the effect of novel rehabilitation therapies and pharmacological agents on reducing spasticity.

1. INTRODUCTION

Animal models of spasticity have recently been developed for the purposes of understanding the underlying cellular mechanisms leading to hypertonia after SCI and developing novel pharmacological and rehabilitation interventions to reduce its debilitating effects [1-3]. However, to date, objective techniques for assessing spasticity quantitatively in these models do not exist. The goal of this project was to develop a sensitive, clinically-relevant measure of spasticity in a rat model of SCI.

2. METHODS

A rat model of spasticity developed by Bennett et al. [2] was used. All experimental protocols were approved by the University of Alberta Animal Welfare Committee. Adult, female Sprague Dawley rats were anesthetized with isoflurane (2-3%) and a laminectomy was performed to expose the sacral spinal cord. A complete transection was induced between S2 and S3, thus paralyzing the tail but retaining bowel, bladder and hind limb function. The back wound was sutured shut in layers and the rats were allowed to recover in a heated cage. The analgesic buprenorphine was administered as needed to ensure a comfortable recovery. Two days to 3 weeks post spinalization, the tails exhibited symptomatic hypertonus, spasms and clonus. The quantification of hypertonus was based on an approach developed by Prochazka et al. [4, 5] for assessing limb rigidity in individuals with Parkinson's disease. It entailed sinusoidally moving the rat's tail at a known amplitude and frequency and measuring the elicited forces.

Elastic (K) and viscous ($B\omega$) stiffness were then computed based on the following muscle model:

$$T = rA(K\sin(t) + B\omega\cos(\omega t)) + C,$$

where T is measured torque, r is the moment arm, A is the angular displacement, K is elastic force stiffness, B is viscosity, and C is a constant. Figure 1 shows raw tail displacement and measured torque records (left) as well as the measured and calculated Lissajous (torque-displacement) graphs (right). The close resemblance between the measured and calculated torques indicates

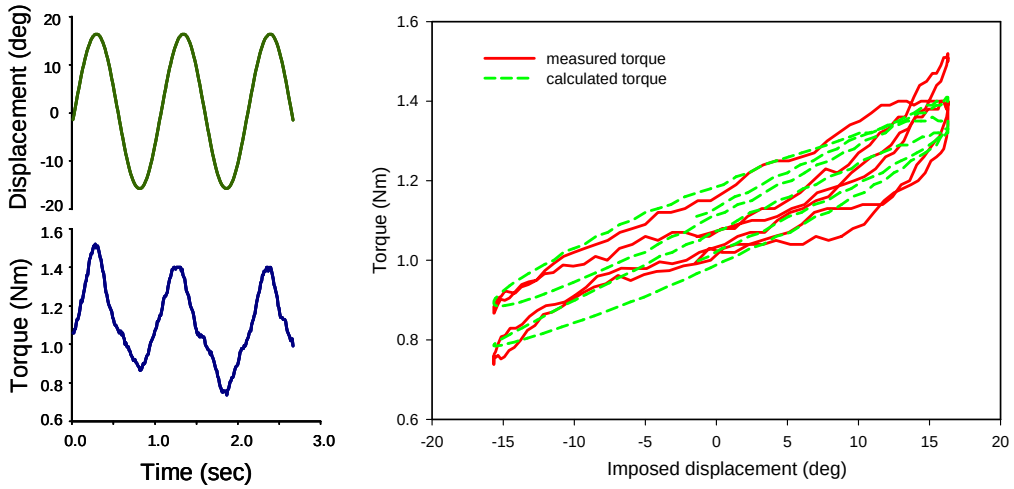

Figure 1. Left: Displacement records imposed by the servo-controlled motor and resulting torque measurements. Right: Lissajous graphs for measured and calculated torque.

the suitability of the muscle model used in this study. Mechanical impedance (Z), the measure of spasticity, is the magnitude of the vectorial sum of K and $B\omega$.

Twelve rats were used to validate the spasticity quantification method. Four days after surgery, and once a week thereafter (up to 4 months), assessments of hypertonus were acquired and compared to measurements obtained under anesthesia (n = 9). Measurements of muscle tone were also compared to those obtained from 3 weight-matched controls.

The measurements were obtained with the rats placed in a standard holding tube. Their tail was attached to a force transducer which was in turn connected to a servo controlled motor. Lateral movements of the tail about the midline were imposed in the horizontal plane and the force transducer recorded the applied force as well as the tail's resistance to stretch. Mechanical impedance was calculated off-line. Different attachment positions (proximal, mid, or distal tail) and frequencies (0.1, 0.5, 1, 1.5 Hz) of imposed movements were used.

3. RESULTS

Mechanical impedance increased over time in spinal rats but remained constant in control rats. In all rats with SCI, the resting impedance was larger than that in control rats (fig. 2). A brief pinch of the tail elicited transient increases in impedance in control

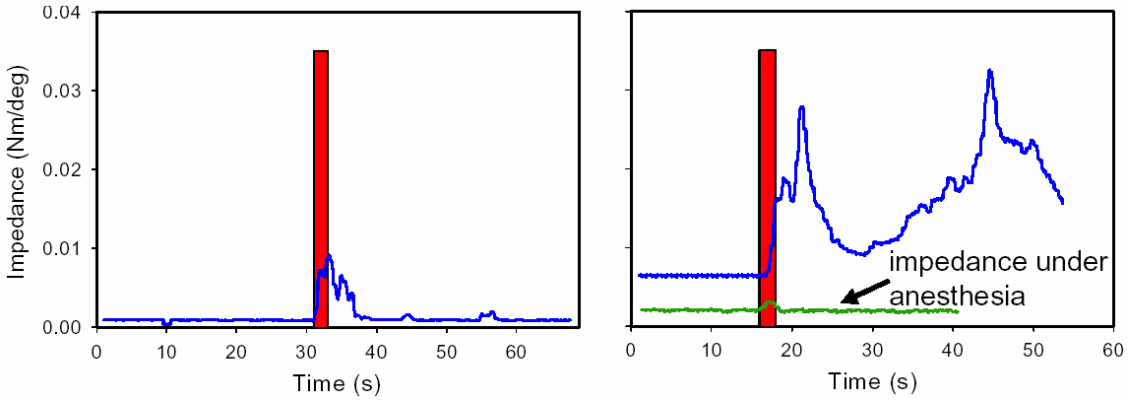

Figure 2. Mechanical impedance measured in a control rat (left) and a rat with SCI (right). The bar indicates the point at which a brief tail pinch was induced.

animals (fig. 2, left) as the rats resisted the stimulus. However, a brief pinch in spinal rats produced large and long-lasting increases in impedance (fig. 2, right). Impedances obtained under anesthesia remained constant in all spinal rats, indicating that there were no changes in passive muscle properties in the 4 month

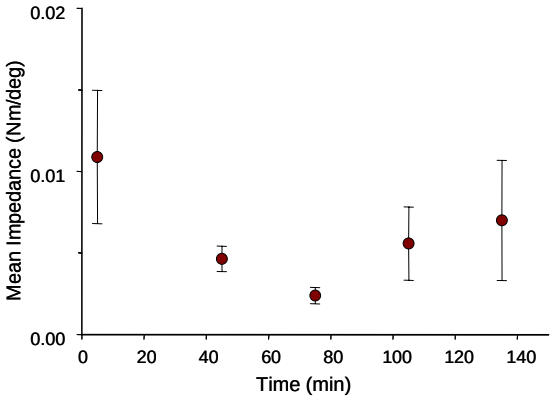

Figure 3. Effect of the administration of baclofen on mechanical impedance in a rat with SCI.

duration of these experiments. The mid-tail position provided the most reliable measurements and tail movements imposed at 1.5 Hz elicited the largest spastic responses. The sensitivity of the method was further assessed by the administration of baclofen (i.p. 6 mg/kg), a commonly used anti-spastic pharmacological agent (fig. 3). There was a clear decrease in the mean and standard deviation of impedance after drug administration followed by an increase as the effects of the drug diminished (ANOVA, $p < 0.05$).

The results indicate that our method for quantifying spastic hypertonus is valid, reliable, and sensitive. We will now use it to investigate the efficacy of electrical stimulation and operant conditioning of the stretch and cutaneous reflexes in reducing spasticity.

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4. DISCUSSION AND CONCLUSIONS