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Therapeutic Effects of Anti-spastic Medication on Neuromuscular Abnormalities in SCI: A System Identification Approach*

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Abstract—**Previous attempts to investigate the effects of anti-spastic medications are limited to clinical studies using that use clinical evaluations to assess. Since these measures are neither objective nor quantitative, the therapeutic effects of such medications on neuromuscular properties have not been fully evaluated. In this study, as a first attempt, we examined the effect of tizanidine, an anti-spastic medication, on modification of the neuromuscular properties of patients with chronic incomplete spinal cord injury (SCI). Each patient was administered 2 mg of tizanidine four times per day for four weeks. The spastic ankle of each patient was evaluated at baseline (prior to any medication, and then 1, 2, and 4 weeks after the start of medication. The ankle was perturbed with a small-amplitude Pseudo-Random Binary Sequence (PRBS) perturbation at various positions over the ankle range-of-motion. A parallel-cascade system identification technique, which provides an objective and quantitative measure of neuromuscular properties, was used to calculate the intrinsic and reflex stiffness. The stiffness *vs.* joint angle trends were then calculated for each evaluation; these curves were compared across the intervention time to determine the recovery pattern (i.e. change over time) due to the tizanidine intervention. All patients exhibited decreases in reflex stiffness (which abnormally increase after SCI) due to the medication; however, patients were observed to exhibit multiple recovery patterns. For some patients, the reflex stiffness continuously reduced over the four-week intervention period, while for other patients, the decrease during the first week (i.e. between the baseline and 1-Week evaluations) was most pronounced. Also, some patients presented a significant decrease with time, while others presented no improvement in the intrinsic stiffness. These findings suggest that tizanidine may be effective in reducing not only reflex stiffness, but also the subject's intrinsic stiffness for certain patients. Future work remains to identify predictors which can objectively determine which patients are likely to exhibit maximal benefit from the tizanidine prior to being prescribed with the medication.**

Keywords—**spasticity, stiffness, reflex, identification, ankle, spinal cord injury, neuromuscular, tizanidine, medication, intervention**

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I. Introduction

Spasticity—a velocity-dependent exaggeration of stretch reflexes—is a common symptom that appears soon after spinal cord injury (SCI), spasticity is a common symptom, occurring in 65-78% of patients [1-3]. Spasticity usually causes pain and fatigue, disrupts daily activity, limits functional ability and results in poor quality of life.

A number of interventions have been developed to manage spasticity, including oral medications, intrathecal baclofen, injection techniques, surgical treatments and physical therapy. One common pharmacological intervention is tizanidine, a central α-2 adrenergic agonist that acts at the spinal and supraspinal levels to effectively reduce muscle tone and spasms in patients with SCI. Several studies have focused on the reduction of spastic symptoms such as hypertonia, spasms, and clonus in SCI patients [4-8]. Our recent work with individuals with chronic spasticity supports this: we found improvements in reflex stiffness after only a single dose of tizanidine [9], suggesting that tizanidine can reduce the spastic hypertonia [4, 10]. Further, although there are some side effects, tizanidine has been shown to be better tolerated by patients compared to other anti-spastic medications [11].

However, those previous studies have primarily assessed spasticity in terms of clinical assessments of spasticity such as the Modified Ashworth Score (MAS) [12-14]. These assessments are inherently qualitative in nature and suffer from inter-examiner variability. Furthermore, no relationship has been found between MAS and intrinsic or reflex mechanical properties. To address this difficulty, we have previously developed a systems identification technique to quantify neuromuscular abnormalities—including reflex and intrinsic stiffness—that are associated with spasticity [15, 16]. We demonstrate that this approach can provide an objective, quantitative measure of neuromuscular dynamics that can be tracked over time in order to study the efficacy of a particular intervention in reducing spasticity [9, 17].

In this study, we apply this technique to examine the effectiveness of tizanidine in reducing reflex stiffness in the chronic incomplete spinal cord injury population. We quantified and tracked the effect of the tizanidine on reflex and intrinsic stiffness over four weeks oral administration of medication.

II. Experimental Protocol

Fifty spinal cord injury (SCI) subjects with incomplete motor function loss and spasticity at their ankles participated in this study. All subjects were injured within their cervical

or upper thoracic (superior to T10) vertebrae. Twenty-five of the subjects were assigned to the intervention (tizanidine) group, while the other twenty-five subjects (aged-matched to the intervention group) were used as control. The control subjects received no intervention. All subjects gave informed consent according to the policies of the Institutional Review Board of Northwestern University.

A. Tizanidine Administration

Subjects were administered 2 mg of tizanidine four times per day for four weeks. Subjects ramped up the dosage up to a maximum dose of 8 mg per day over the first week; this full dosage was maintained for the subsequent three weeks.

B. Experimental Setup

A custom joint stretching apparatus was used to apply a controlled-position perturbation to each subject's ankle. Subjects were seated and secured in an adjustable chair with the ankle strapped to the foot rest and the thigh and trunk strapped to the chair. The seat and foot rest were adjusted to align the ankle axis of the rotation to be coincident with the center of the motor shaft (Fig. 1).

Joint position was recorded by a rotary encoder, while a six-axis torque transducer recorded joint torque about the center of ankle rotation. Electromyograms (EMGs) placed at the tibialis anterior (TA) and gastrocnemius (GS) were recorded using bipolar surface electrodes. These signals were sampled at 1 kHz by a 16 bit A/D converter, and low-pass filtered at 230 Hz on-line to prevent aliasing.

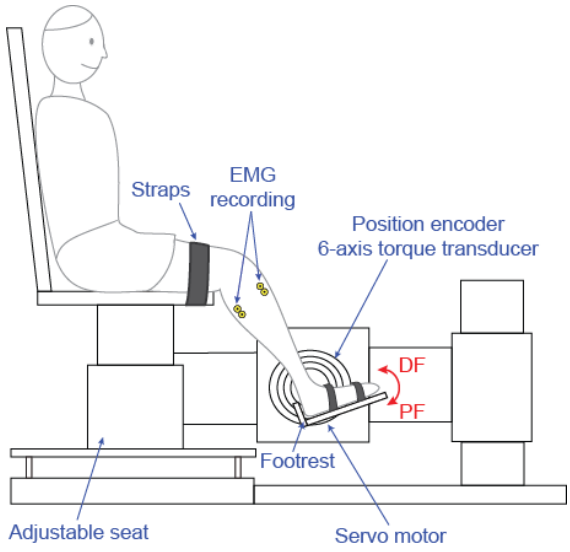

Fig. 1: Experimental setup

B. Experimental Procedure

The servo motor applied a series of pseudorandom binary sequences with an amplitude of 0.03 rad and a switching-rate of 150ms to perturb the ankle at various positions over the ankle range of motion, at 5° increments.

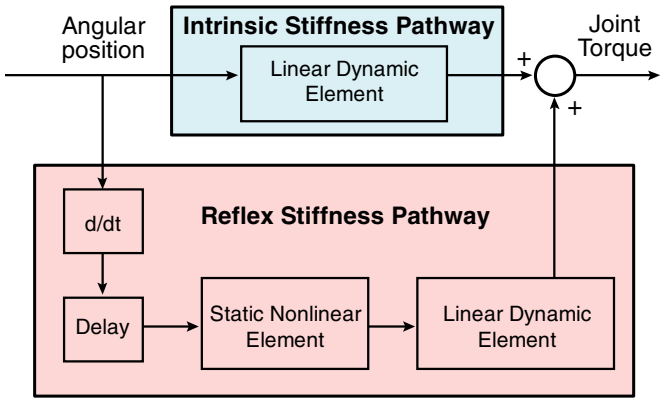

Fig. 2: Parallel-cascade system identification model.

During this time, the knee was held at 30° flexion. The ankle neutral position (NP) was defined at 90° and defined as zero for this study. Plantarflexion was considered negative by convention.

The ankle which was considered more spastic— as determined by the MAS [12-14]— was used for evaluation. The perturbations were performed while the subject was in the passive state, i.e., no active contractions were performed. An oscilloscope recording the EMG in real-time was used to verify there were no active contractions; if they were detected, the perturbation was repeated.

Subjects received the full battery of perturbations four times: at the baseline (i.e. immediately prior to the first tizanidine dose), and 1, 2 and 4 weeks after the start of tizanidine administration.

III. Analytical Methods

A. Parallel-Cascade System Identification Technique

Intrinsic and reflex contributions to the ankle stiffness dynamics were separated using a parallel-cascade identification technique [15, 16]. Intrinsic stiffness dynamics were estimated by determining the Impulse Response Function (IRF) between position and torque, using Hammerstein identification methods (Fig. 2). A second-order model with mass *I,* viscosity *B,* and stiffness *K* was fit to the IRF; *K* was the parameter of interest and tracked over time. Reflex stiffness dynamics were modeled as a differentiator, in series with a time delay, a static nonlinear element (a half-wave rectifier in velocity) and then a third-order dynamic linear element with stiffness gain *G,* undamped natural frequency ω_n, damping coefficient ζ, and first-order pole *p*; the gain *G* –relating velocity to reflex-torque—was used as the reflex stiffness and was tracked over time. This analysis was performed separately for each of the evaluated ankle positions, yielding reflex stiffness vs. angle and intrinsic stiffness vs. angle curves for each experimental trial.

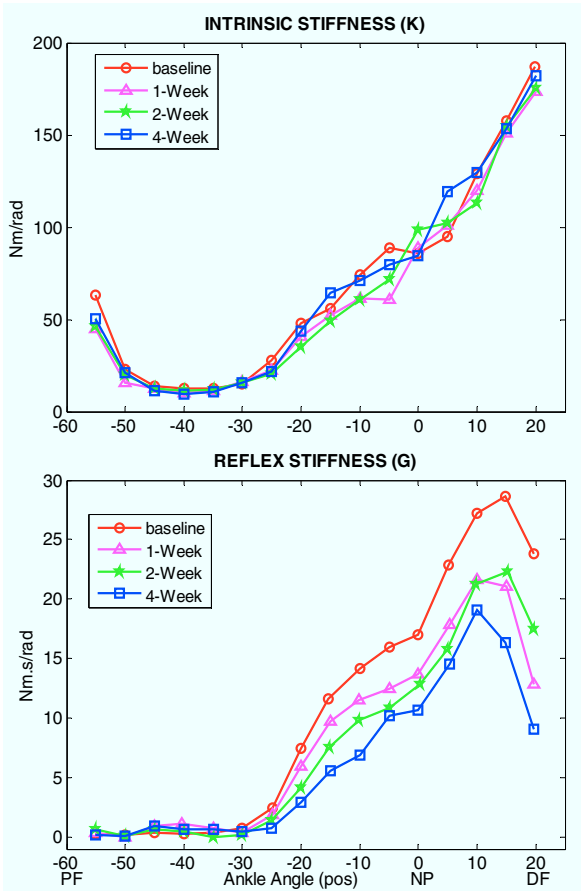

Fig. 3: Intrinsic and reflex stiffness trends for Subject A.

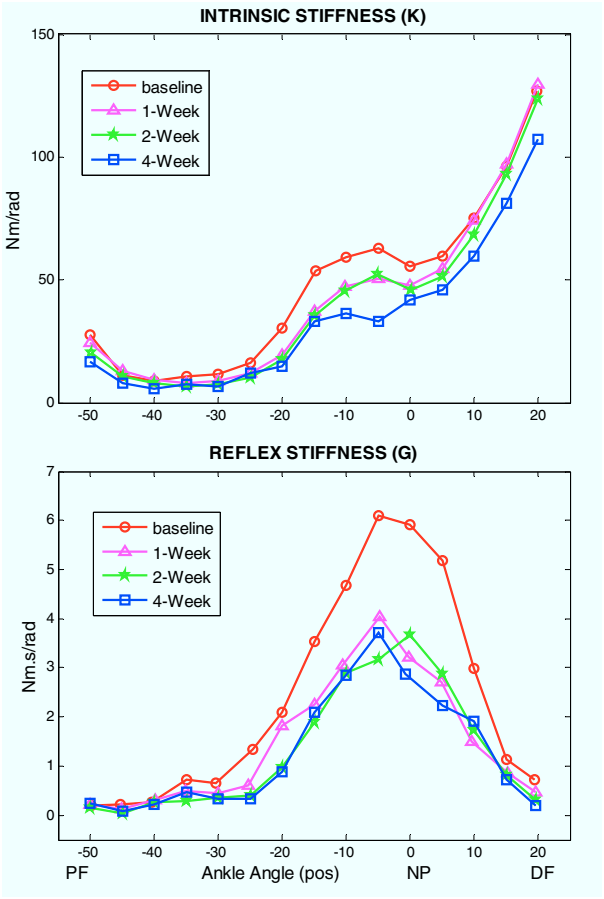

Fig. 4: Intrinsic and reflex stiffness trends for Subject B.

IV. Results

Stiffness vs. joint angle curves were generated for each of the tested subjects. It was observed that not all subjects exhibited similar trends in time (i.e., recovery patterns); rather, recovery patterns differed between subjects. For example, some subjects in the intervention group exhibited little change in the intrinsic stiffness (K) over the study period while others presented marked improvements in intrinsic stiffness with time. Consider, for example, two representative subjects A and B. Subject A (Fig. 3) showed no change in K over the four weeks of tizanidine. Meanwhile Subject B (Fig. 4) showed a substantial decrease in K over time; in fact, the subject exhibited a pronounced drop in intrinsic stiffness in the first week of dosage (i.e. between the baseline and 1-Week measures), exhibited little change during the second week (between 1-Week and 2-Week), and then exhibited another pronounced drop in stiffness in the last two weeks of tizanidine (between 2-Week and 4-Week evaluations).

For the reflex stiffness, most subjects exhibited a decrease in reflex stiffness over time, which was expected as the tizanidine is an anti-spastic medication. However, not all subjects experienced the same pattern of change in response to the intervention. Some subjects (e.g. Subject A) exhibited continuous reductions in stiffness with time (Fig. 3). Other subjects (e.g. Subject B) presented a large reduction in stiffness (~50%) in the first week (between baseline and 1-Week observations); and only minimal further reductions in reflex stiffness over the subsequent three weeks.

For the control group, no significant changes in time for either the reflex stiffness or the intrinsic stiffness occurred.

V. Discussion

In this study, we examined, for the first time, the therapeutic effects of an anti-spastic medication (tizanidine) on neuromuscular abnormalities—specifically on the intrinsic and reflex stiffness—for patients with incomplete SCI.

We observed that tizanidine consistently produced a decrease in reflex stiffness over four weeks of administration. Thus we have quantitatively shown that the reflex stiffness is reduced by the tizanidine, as was expected since tizanidine is designed to selectively modify reflex responses after neurological disorders [6, 9, 18, 19].

However, we also found quantitatively that the intrinsic stiffness was reduced in some patients due to the medication. The decrease in intrinsic stiffness, could be due to changes in the ankle joint functional condition—including changes to the length-tension curve which can occur secondary to injury due to various factors, including spasticity. Reducing spasticity thus can consequently modify the functional condition, causing intrinsic stiffness to be

reduced.

Based on our findings, not all subjects exhibited a uniform change over time (recovery pattern); rather some subjects saw a consistent decrease in reflex stiffness while other subjects exhibited a substantial decrease in stiffness between the baseline and the first week of medication, and then a lower decrease over the remaining weeks of the intervention period. This difference suggests that subjects should not be evaluated as a single homogeneous group when modeling the subject response to tizanidine, but rather a longitudinal classification scheme, such as Growth Mixture Modeling (GMM), should be employed [20-25]. Such an approach can partition subjects into multiple distinct classes based on similar recovery patterns; the recovery patterns within each class can then be modeled separately. Applying GMM to these subject responses is the subject of a future study.

VI. Conclusion

The efficacy of tizanidine in reducing neuromuscular abnormalities for patients with incomplete spinal cord injury was quantified for the first time. The results indicate that our system identification technique can be a powerful and objective tool to quantify the effects of therapeutic interventions or treatment on neuromuscular properties in patients with SCI or other neurological disease.

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