# Classifying and predicting endurance outcomes of $\alpha_2$-adrenergic agonist intervention in spinal cord injury.

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***Abstract*—Spinal cord injury (SCI) is a traumatic condition that can lead to both functional and neuromuscular impairments. Spasticity in the muscles surrounding the ankle joint caused by hypertonia is often reported as a complication. We investigated whether a pharmacological intervention using Tizanidine, an anti-spastic medication acting as an $\alpha_2$-adrenergic agonist, could lead to improvements in walking endurance. We placed subjects on a 4-week program and measured the change in clinical measures of walking speed, endurance, and mobility. We used growth mixture modeling (GMM) to class subjects into groups based on recovery patterns. Two classes of recovery were found by GMM: high and low functioning. Radom coefficient regression (RCR) was then used to identify significant changes over time. Statistically significant improvements in walking endurance were shown for the high functioning group. However, a small number of subjects in the high functioning group showed improvement greater than the smallest real difference (SRD), which indicates a clinical significance as well. We also investigated the extent to which these recovery patterns can be predicted using baseline measures. Baseline walking endurance was found to be a robust predictor of recovery in walking endurance. Subjects that began the intervention with already higher endurance showed a greater chance of improvement in endurance over time. This information could potentially be used as a fast and reliable assessment tool for clinicians to predict which patient can benefit the most from this intervention prior to prescribing the medication, and thus optimizing cost and resources. Our findings demonstrate that these techniques can be used to characterize and predict the progress of changes to functional impairments due to various types of intervention.**

***Keywords*—spasticity, gait, recovery, tizanidine, intervention, medication, modeling, prediction, treatment, spinal cord injury, endurance, locomotion**

## I. Introduction

Individuals affected with spinal cord injury (SCI) can show significant impairment in a variety of functional tasks, including walking. This has led to many studies and rehabilitation programs that specifically target functional improvement after SCI.

In addition to functional impairments, neuromuscular complications often arise as a result of SCI as well. Hypertonia (the defining feature of spasticity) of the muscles surrounding the ankle joint has been one of the main self-reported complications post SCI [1]. The ankle joint and surrounding muscles play an especially important role during walking, and also contribute to other functional tasks [2]. Spasticity can also be a burden on daily activities, adding increased physical, emotional, and social costs [3, 4].

There is still debate as to how spasticity is actually related to functional impairment. Some studies have shown that increased spasticity leads to higher functional impairment [5-7]. However, other studies have shown that decreased spasticity may not necessarily lead to functional improvement across the board [8, 9], but can show improvements in mechanical reflex responses [10].

Tizanidine is an anti-spastic drug acting as an $\alpha_2$-adrenergic agonist that is used as a muscle relaxant. Tizanidine has been shown to reduce levels of hypertonia at least as effectively as other anti-spastic medications [11-15], with similar or milder side effects [16-18]. It has also been shown to improve locomotor capacity in spinalized cats [19].

When measuring functional improvements after incomplete SCI, the results can be highly variable. When selecting patients for clinical intervention it could be of great multi-disciplinary benefit to be able to predict which subjects have the best chance of improvement in a specific intervention. This could save valuable time, effort, and money, as well as avoiding potential side-effects, by not putting patients through interventions in which they have little chance of showing improvement.

Recently, we have used a technique called growth mixture modeling (GMM) to classify recovery patterns in rehabilitation research [20]. GMM is widely used in psychological and educational research to separate large datasets into smaller, similar groups. This technique works by grouping subjects based on their baseline scores, and also their trend in recovery patterns over time [21, 22]. This allows the identification of distinct recovery classes, and the potential for baseline data to be used as a predictor for class membership, before entering into a treatment program. In our earlier studies, we characterized the therapeutic effects of robotic-assisted locomotor training on SCI subjects using the GMM technique, and identified ankle isometric maximum voluntary contractions at baseline as significant predictors [20].

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To evaluate the clinical significance of the results, in addition to being statistically significant, the therapeutic effects must be clinically meaningful. For this we will also consider which subjects achieved an improvement greater than the smallest real difference (SRD). This is the smallest improvement to detect real, clinical change [23].

Our main objective was to quantify the therapeutic effects of Tizanidine on gait impairment in SCI subjects with incomplete motor function loss. We investigated whether GMM was able to identify recovery patterns of major clinical measures of gait impairment. We used random coefficient regression (RCR) to determine if subjects in these recovery classes showed significant change. We then looked for a baseline measurement that could be used as a significant predictor for these classes.

## II. Methodology

### A. Subjects

Subjects with incomplete spinal cord injury, as a result of trauma, were recruited from the outpatient service at the Rehabilitation Institute of Chicago. Subjects were randomized into two groups. One group received pharmacological intervention (Tiz group, n = 26) and the other was a control group (n = 29). All subjects provided written informed consent and the study had ethical approval from the Northwestern University Institutional Review Board.

### B. $A_2$-adrenergic Agonist Intervention

The intervention was provided over a four week period. Subjects were administered 0.3mg/kg of Tizanidine orally four times per day for the entire four week intervention. Baseline data was collected before the subjects were administered Tizanidine dosage. Outcomes were measured at baseline, one, two, and four weeks into the intervention.

The clinical outcome measures performed for this analysis were three different functional walking tests. The six-minute walk test (6MWT) is a test of endurance where subjects are asked to walk for six consecutive minutes and the distance travelled is measured in meters. Timed up-and-go (TUG) is a test where subjects are asked to start sitting in a chair, stand up, walk 3 meters out and back, and then sit back down as quickly as they can. The ten meter walk test (10MWT) requires subjects to cover a 10-meter span as quickly and safely as possible.

## III. Data Analysis

Data were classified using growth mixture modeling (GMM) [21, 22] and random coefficient regression (RCR) [24] modeling. The GMM can be used to capture heterogeneity in developmental pathways and assumes that the population can be divided into a finite number of latent classes (homogeneous inter-subject subpopulations) by inspecting the intra-subject difference in growth pattern. The quality of the resulting classification was evaluated by the posterior probabilities of class membership among subjects. The Bayesian Information Criterion (BIC) determines the model performance. Subjects were assigned to the latent class in which they had the highest posterior membership probability.

The RCR modeling [24] was applied in each latent class to define the growth pattern, with the baseline measure considered as a covariate. Such a model allows for individual difference in the response function to accommodate inter-subject variability.

Clinical improvement was calculated as the difference in scores in the clinical measurements between the final time point, and the baseline. Those subjects that improved beyond the smallest real difference (SRD) were noted.

## IV. Results

### A. Therapeutic Effects of Tizanidine on Gait Impairment

Results from the GMM placed subjects (from both the control group, and the Tizanidine group) into 2 classes: low-functioning (Class 1) and high-functioning (Class 2) for all three clinical measures. In the Tizanidine group for 6MWT, random coefficient regression shows that the subjects in class 2 achieved a significant change over time (slope = 7.060 m/week; $p = 0.015$), while the subjects in class 1 did not (slope = 1.415 m/week; $p > 0.05$). Also, there were three subjects that achieved improvements greater than the SRD, and these subjects were all correctly placed into class 2 by the GMM.

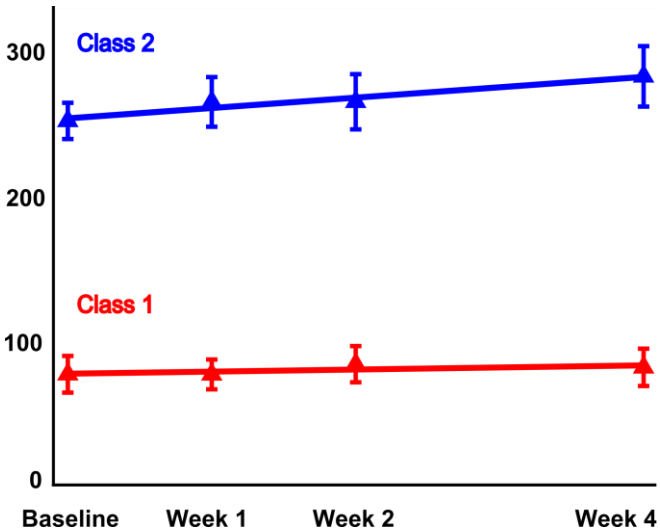


Figure 1: Mean (±SE) distance travelled (m) during 6MWT at each time point. Subjects were classed into two groups using GMM and regression was done using RCR.

In the Tizanidine group, no significant change over time was found in recovery classes for both the 10MWT, and TUG clinical measures. Based on this, only data from the 6MWT is presented.

In the control group, performing the same tests under no intervention did not show significant change over time for any of the three clinical measures.

### B. *Prediction of Recovery Patterns for 6MWT*

The subjects that were grouped into class 2 all showed higher baseline 6MWT scores that those grouped into class 1. Lack of overlap between two classes provided the ability to predict the recovery patterns of 6MWT using its baseline score as a predictor. There was a clear division at a score of approximately 175 m on the baseline test. All class 1 subjects scored below this value, and all class 2 subjects scored above this value. Class 1 (n = 9; mean = 76.04 ± 45.44) contained slightly fewer subjects than class 2 (n = 13; mean = 243.9 ± 44.2). These results indicate that subjects with walking endurance of 175 m or higher at baseline will be more likely to belong to class 2; that is, their walking endurance will improve over time. Subjects who could not complete the 6MWT due to ability, or time constraints, have been omitted.

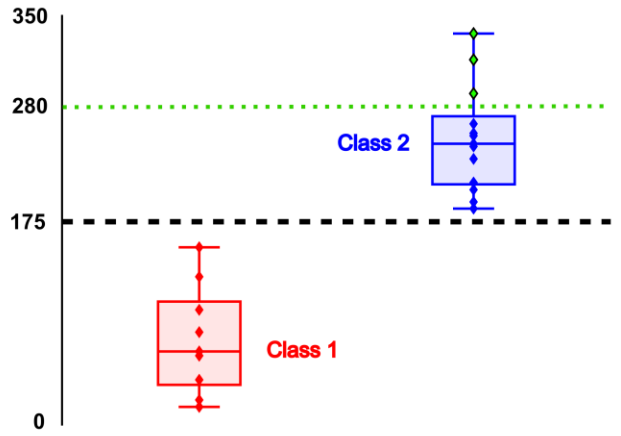


Figure 2: Baseline 6MWT (m) scores separated by GMM class. Box plots for each class are shown to illustrate distributions. Individual points represent baseline scores for individual subjects (n=26). All subjects who were placed into class 2 also scored above 175m (black dashed line). Subjects above 280m (green dotted line) achieved improvement greater than the SRD.

## V. Discussion

The focus of this study was to investigate whether a Tizanidine intervention could provide significant improvement in walking impairment in patients with incomplete spinal cord injuries. GMM was used to class subjects into groups based on their recovery patterns for the clinical tests. RCR analysis revealed significant improvement in walking endurance for the high functioning class of the Tizanidine group. This implies that Tizanidine may be an effective intervention for improving endurance in higher functioning subjects.

The effect of anti-spastic pharmaceuticals on functional walking outcomes is an area that has been understudied. There have been reports of small effects on walking speed due to Tizanidine [25], however there have been no reports of any effects on walking endurance. Recently, we have shown Tizanidine to be effective in reducing reflex stiffness of the ankle group muscles [10]. We speculate that the ability to walk for longer durations could be due to reduced spasticity in the gastrocnemius muscle. This decrease in spastic activity potentially allows the tibialis anterior muscle to improve coordination with other muscles during the gait cycle. Further study is required to investigate this relationship.

There were also 3 subjects who showed clinical improvement greater than the SRD. These subjects showed clinically and statistically significant improvement throughout their intervention. All 3 of these subjects were correctly classed as high functioning by the GMM, and posted baseline scores that were the highest of the Tizanidine group (> 280 m). This implies that Tizanidine intervention may be the most useful in patients that are already very high functioning. We found no other discernible differences between high functioning subjects who achieved SRD versus those who did not. A possible explanation for this could be subject motivation and pain levels. We did not monitor these effects on patients, however those subjects who experience more chronic pain are likely to be less motivated and more distressed [26]. The psychosocial factors of pain and having a difficult condition could also play a role in their motivation [27]. This could potentially lead to a decrease in effort and overall improvement throughout the intervention. However, further study is required to investigate this speculation.

We also investigated the extent to which these recovery classes from GMM could be predicted, using baseline data. Our results show that the baseline 6MWT score is a strong indicator of recovery pattern. Subjects who scored higher on their baseline 6MWT were more likely to be placed into class 2, and therefore are more likely to see significant improvement. Such findings indicate that a baseline 6MWT score can be a reliable and fast clinical test that can be used to determine which subjects are most likely to see an increase in their walking endurance if placed into a 4 week Tizanidine intervention, prior to being placed on any medication.

The clinical significance of being able to place subjects into interventions more effectively cannot be overstated. Having some idea of the chance a patient has of improving during a particular intervention could be very valuable in the clinical field. It could potentially save time and resources by not putting patients through unneeded and ineffective drug interventions, as well as potentially harmful and inconvenient side effects from medication.

## VI. Conclusion

Our study reveals that Tizanidine intervention can be an effective way to improve walking endurance in higher functioning subjects. GMM was used to classify subjects into higher and lower functioning classes, and all subjects that achieved the SRD were grouped correctly into the higher functioning class.

Also, our findings show that a baseline 6MWT may be a fast and reliable clinical assessment that can be used as a predictor for recovery patterns. This could allow clinicians to quickly determine the best course of action for an individual with incomplete SCI, while keeping costs and unnecessary procedures to a minimum.

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