Effects of the Addition of a Single Bout of Whole-Body Vibration to a Single Bout of Treadmill Training on Gait and Spasticity in Ambulatory Children with Cerebral Palsy

PROJECT PLAN

Introduction:
Cerebral palsy (CP) is defined as “a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.” It is the most common motor disability in childhood, occurring in between 1.5 and 4 per 1,000 live births worldwide. The most common presentation of CP is spastic, representing approximately 80% of individuals, and is characterized by a type of hypertonia known as spasticity. The presence of spasticity in CP frequently correlates with the presence of impairments such as muscle weakness, contracture development, and stereotypical gait abnormalities. Spasticity has long been considered to be the cause of these impairments in many children with CP, even though a causal relationship is not well-supported in the literature. Nearly 60% of children with CP walk independently, but abnormalities of gait represent a significant issue for most of this population. These gait abnormalities are associated with decreased participation in age-appropriate activities and social roles, and decreased quality of life in these children.

Treadmill training (TT) is one of the most commonly utilized rehabilitation techniques in pediatric rehabilitation such as children with CP, although evidence regarding its efficacy in improving gait in this population is inconclusive. Walking on a treadmill provides a repetitive stimulus for stepping, allowing for consistent, task-specific and forced practice of ambulation, and often leads to better walking patterns compared to overground gait training. However, the improvements in gait after months-long TT are inconsistent and often too small to be clinically significant; additionally, there is little evidence to show that spasticity is reduced after TT in children with CP. Without specifically targeting spasticity reduction before TT, the training may simply be reinforcing a non-ideal gait pattern. Injections of botulinum toxin type A (Botox), a neurotoxin that causes transient chemical denervation, have been found to improve the gait patterns and motor function of children with CP when combined with physical therapy. This suggests that combining spasticity-reducing treatments with therapeutic interventions may increase their effectiveness in improving functional abilities. However, Botox is invasive, and its effectiveness may decrease with repeated use. It would thus be ideal to explore a non-invasive therapeutic paradigm which can be used to reduce spasticity before TT to augment potential training outcomes in children with CP.

Single bouts of whole-body vibration (WBV) appear to be safe and well-tolerated in children with CP. This paradigm has been found to decrease spasticity and improve isolated active ROM at the knee and ankle. Further, single bouts of WBV improve gait parameters such as walking speed and stride length in children and adults with CP. While these effects are transient, lasting between ten minutes and two hours, they are still clinically relevant. This suggests that clinicians could take advantage of the transient improvements in spasticity and gait parameters following WBV by immediately presenting a single bout of TT, reinforcing the improved gait pattern and eliciting the translation of this new pattern to overground walking as motor learning occurs. This may potentially help children with CP participate more fully in exercise and daily activities. However, to date, the efficacy of this combination has not been investigated in the literature.

Spasticity is currently thought to be a combination of (a) passive stiffness derived from the viscoelastic properties of spastic tissues, (b) hyperreflexia of the stretch reflex, and (c) poor descending cortical control of the stretch reflex. However, the mechanisms of spasticity are still not fully understood, and the clinical instruments used to quantify it such as the Ashworth
Effects of the Addition of a Single Bout of Whole-Body Vibration to a Single Bout of Treadmill Training on Gait and Spasticity in Ambulatory Children with Cerebral Palsy

scale have questionable validity and specificity and fail to address the mechanisms of spasticity. This has led to the development of instrumented spasticity measures\textsuperscript{21,22}, which combine kinematic and electromyographic (EMG) data to more comprehensively assess spasticity.

Machine learning is a powerful tool that can be employed to better understand gait patterns. Features, which are measurable properties or characteristics of the data, are an important aspect of machine learning. The spectrum of machine learning techniques ranges from classical linear regressions to deep neural networks. Neural networks, in particular, can be used to synthesize features from raw input data and automatically extract the most important components of the data. This can be used to elucidate useful information about the data that would otherwise have gone undetected. Because data describing human biomechanics is often complex and high-dimensional, machine learning tools can be used to reveal practical information about this data. Statistical techniques have primarily been used to classify or diagnose different gait pathologies. For example, predictive modeling, in which input data is mapped to a particular disease, and data mining, which can be used to find different subpopulations within a pathology, are common machine learning practices in biomechanics. Despite some recent work, little research has been conducted that uses these tools to discover the underlying mechanisms that contribute to these pathologies.

Therefore, this study aims to determine if a single bout of TT following a single bout of WBV will produce more acute improvements in the spasticity and gait pattern in children with CP than a single bout of TT alone. Further, we aim to understand the aspects of spasticity affected by these interventions using an instrumented spasticity assessment. Finally, we aim to investigate the mechanisms by which these interventions cause improvement by utilizing a machine learning approach to identify salient features that differentiate our subjects’ gait data pre- and post-intervention from previously collected gait data of typically developing children.

Goals and Aims:
Aim #1: To determine if a single bout of TT following a single bout of WBV will be more effective at producing acute improvements in the overground gait and lower extremity spasticity of children with CP than a single bout of TT alone.

Hypothesis 1: OG gait parameters, including spatiotemporal and kinematic parameters, and muscle co-contraction patterns will improve to a greater extent following a single bout of TT preceded by WBV than following a single bout of TT alone.

Hypothesis 2: WBV will affect spasticity by decreasing passive stiffness, as measured by the pendulum test, and by decreasing the hyper-excitability of the stretch reflex, as measured by a decrease in EMG and torque changes between low and high velocity movements during the modified Tardieu scale (MTS).

Aim #2: To develop a classifier which can determine the salient features that differentiate the gait patterns of children with CP pre- and post-intervention with WBV and TT and determine if their gait patterns post-intervention more closely resemble typical gait.

Hypothesis 3: Features that have clinically been shown to differ such as dynamic ankle ROM and muscle activation patterns will be salient.

Hypothesis 4: The gait patterns of children with CP following intervention with WBV and TT will be more similar to typical gait than to their baseline gait, as measured by $R^2$ correlation and alpha divergence.
Effects of the Addition of a Single Bout of Whole-Body Vibration to a Single Bout of Treadmill Training on Gait and Spasticity in Ambulatory Children with Cerebral Palsy

Methodology:
Participants

We aim to recruit 20 ambulatory children with CP between the ages of 6-17 based on the preliminary data collected from another WBV project in the Biomechanics lab at Georgia State University. Inclusion criteria include a medical diagnosis of spastic CP, a Gross Motor Function Classification System (GMFCS) level of I, II, or III, and an age of 6-17 years at the time of data collection. Exclusion criteria include a history of Botox injections to the lower extremities within the past 3 months, a history of musculoskeletal injury within the past 6 months, a history of lower extremity orthopedic surgery within the past 6 months, a history of significant uncontrolled cardiac abnormalities, a history of uncontrolled seizures, and any cognitive or behavioral issues that prevent following instructions during treadmill walking.

Experimental Protocol

This is a self-controlled study. All data will be collected during a single visit to the lab at Georgia State University. Following informed consent and assent, subjects will have their height, weight, and other anthropometric measures taken. Sixteen reflective markers will be placed on the landmarks for the Plug-In Gait Lower Body model using double-sided tape. Trigno surface EMG blocks (Delsys, Natick, MA) adhered over the following muscles: vastus lateralis, biceps femoris, tibialis anterior, and lateral gastrocnemius. Previous work in my lab has shown that the transmission of vertical acceleration from WBV is significantly reduced above the knee\(^2\), so this study will focus on the knee and ankle joints.

The subject will complete 3 trials of walking 10 meters overground at a comfortable pace, which will be averaged to determine each subject’s “self-selected” speed used to calculate the TT speed for each subject. The subject will then perform 3 repetitions of a maximum voluntary isometric contraction of each muscle group listed above, which will be averaged and used to normalize EMG data.

Next, spasticity of the gastrocnemius and biceps femoris will be assessed using the MTS. The MTS is a measure of spasticity that involves an examiner passively moving a joint at high and low velocities; the ROM at both velocities is recorded, as is a subjective rating of the degree of spastic “catch.” The subject will then complete 3 trials of overground walking at a self-selected pace through our camera field. During these tasks, motion data will be collected using the 8-camera Vicon motion capture system (Vicon, Denver, CO) and EMG data will be collected from all surface EMG electrodes. The subject will move to a treadmill and complete 10 minutes of TT at 110% of their self-selected overground speed. Following this, the subject will repeat the MTS and overground walking.

Next, the subject will take a 15-minute seated rest to wash out any residual effects or fatigue from the TT; to our knowledge there are no reports of lasting acute effects following a single bout of TT, so we expect this wash-out period will provide sufficient time to return to baseline. Following the rest, spasticity will be re-assessed using both the pendulum test and the MTS. The pendulum test assesses passive stiffness of the knee by measuring the degree of oscillation of the lower leg after an examiner passively straightens and releases the limb. The subject will then repeat 3 trials of overground walking.

The subject will then move to a Galileo Med-L side-to-side-alternating WBV plate (StimDesigns LLC, Carmel) and complete 8 bouts of 90 seconds of vibration at 20 Hz and an amplitude of 2 mm. Between bouts, the subject will rest in a seated position for 90 seconds. After the final bout of vibration, the subject will repeat the pendulum test, MTS and
overground walking. Immediately after this, the subject will complete a second 10-minute bout of TT as before. Following this, the subject will repeat the pendulum test, MTS, and overground walking. Each visit is expected to take approximately 2 hours (Fig. 1).

Data Analysis and Outcome Measures

For hypothesis #1, outcome measures will include (1) spatiotemporal parameters including walking speed and stride length, (2) peak joint angles at the knee and ankle, (3) co-contraction indices at the knee and ankle, as described by Gross et al.24, and (4) MTS scores, performed using standardized procedures.25

For hypothesis #2, outcome measures will include (1) the first swing excursion and relaxation index of the pendulum test, and (2) spasticity-related “change” parameters during the MTS, as described by Bar-On et al.21, including percent integrated EMG change, torque change, and work change. These variables represent the difference in muscle activity, rotational force, and work, respectively, between a high-velocity and a low-velocity passive movement. Lower change scores representing less spasticity.

For hypothesis #3, we will apply machine learning techniques such as deep neural networks and support vector machines to explain how the gait data from our subjects differs from typical gait data. Outcome measures will include the $R^2$ correlation between the two datasets and alpha divergence, which can be used to determine the similarity between the model representing typical gait and our subjects’ gait post-intervention. Further, we will compare meta parameters of the models to understand clinically significant differences between the sets of data.

For hypothesis #4, we will determine which features are most discriminative between pre- and post-intervention gait. To determine feature importance, we will measure the change in the model’s prediction error after permuting each feature; the features that cause the most error after permutation contribute the most to the differences in the gait26, lending insight into which features are most salient. A blend of expert, human-engineered features combined with deep learning features will be used to create a better model and construct a classifier to identify salient features which are discriminative yet interpretable.

Statistical Analysis

We will use SAS 9.4 (SAS, Cary, NC) for statistical analysis of our first two hypotheses. For hypothesis #1, two-way repeated measures ANOVAs (2 protocol x 2 time) will be used on gait parameters and MTS scores to conduct pretest-posttest comparisons between the two TT protocols. I propose that an interaction between protocol and time will be found, with a greater improvement in gait parameters and MTS scores after the bout of TT following WBV. For hypothesis #2, dependent t-tests will be used on the relaxation index and spasticity change parameters before and after WBV. We propose that WBV will improve the relaxation index as well as each of the spasticity change parameters. A significance level of $\alpha = 0.05$ will be used.

Anticipated Results:

Hypothesis #1: We expect that overground spatiotemporal parameters will remain relatively unchanged following the bout of TT alone, will improve after the bout of WBV, and will improve further following the second bout of TT immediately following WBV. We expect a similar pattern to emerge with regard to peak joint angles and muscle-co contraction patterns. Specifically, we expect to see increased walking speed, increased step length, increased dynamic range of motion at the ankle, and decreased muscle co-contraction about the ankle and knee.
Hypothesis #2: With regard to spasticity, we expect that changes in muscle tone will occur in all three theoretical components: (a) passive stiffness derived from the viscoelastic properties of spastic tissues, (b) hyperreflexia of the stretch reflex, and (c) poor descending cortical control of the stretch reflex. Specifically, we expect a decrease in hyperreflexia and an increase in voluntary muscle control following WBV that will persist or continue to improve following the second bout of TT.

Hypothesis #3: We expect to see a greater $R^2$ correlation between post-WBV and TT and typical gait versus post-WBV and TT and baseline. Fig. 2 represents what we might expect to see if the $R^2$ value is greater than zero for different dimensionalities of features. We expect to see a similar result when comparing the models using alpha divergence, with the meta parameters for post-WBV and TT gait being more like the parameters for typical gait. We expect both the $R^2$ values and meta parameters for gait post-TT alone to be more like those of baseline gait.

Hypothesis #4: We expect that features such as dynamic ankle ROM and normalized EMG activity (including increased burst and decreased tonic firing) will be salient. Salient expert-engineered features are easier to predict than features from deep neural networks. The features learned from a neural network will likely be more abstract but will still lend insight into the salient parts of the data.

Impact on healthcare delivery:

Our proposed study differs from typical literature focused on the relative efficacy of therapeutic paradigms in that we also aim to investigate the specific neuromuscular mechanisms responsible for the observed functional changes. Although WBV has been reported in the literature to have positive effects on the spasticity and motor function of individuals with neuromotor disorders the mechanisms are still unclear. When choosing rehabilitation techniques for a population as heterogeneous as CP, it is critical to understand exactly which aspects of the neuromotor system a given intervention is acting on. By utilizing a multi-faceted approach that incorporates typical gait parameters (such as joint angles and spatiotemporal parameters) with an instrumented measure of spasticity and a machine-learning approach, this study is uniquely able to quantify both the functional changes seen following WBV and TT as well as provide insight into the mechanisms behind those changes. This will allow us to provide valuable information about the contribution of spasticity to various aspects of abnormal gait in children with CP, and how interventions such as WBV can modulate those effects. If, as we suspect, WBV is effective at transiently managing spasticity in children with CP and improving their gait patterns during TT, this represents a novel and non-invasive treatment paradigm that has the potential to significantly improve the walking abilities of children with CP without the need for regular BTX-A injections. Additionally, information we discover about the mechanisms by which WBV modulates spasticity may further our limited understanding of how exactly spasticity affects the development of stereotypical gait patterns in children with CP. Finally, our incorporation of machine learning to analyze changes in gait parameters may uncover clinically-relevant effects of WBV that have not been previously reported in the literature.
Effects of the Addition of a Single Bout of Whole-Body Vibration to a Single Bout of Treadmill Training on Gait and Spasticity in Ambulatory Children with Cerebral Palsy

FIGURES

Fig. 1: Visual representation of experimental protocol

D=1

D=2

D=3

Fig 2. Graphical representation of the classes of data where the data has been reduced to one, two and three dimensions to simplify data representation
Effects of the Addition of a Single Bout of Whole-Body Vibration to a Single Bout of Treadmill Training on Gait and Spasticity in Ambulatory Children with Cerebral Palsy

REFERENCES


Effects of the Addition of a Single Bout of Whole-Body Vibration to a Single Bout of Treadmill Training on Gait and Spasticity in Ambulatory Children with Cerebral Palsy


