EVALUATING TWO MEASURES OF POSTURAL STABILITY IN RESPONSE TO PERTURBATIONS IN PEOPLE WITH DIABETIC NEUROPATHY

By
Matthew G. Becker
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Director of Thesis: Paul DeVita, Ph.D.
Major Department: Kinesiology

Diabetic neuropathy is a common complication of diabetes. It is characterized by a marked decrease in proprioception, particularly in the lower body. This reduced proprioception leads to an increase in falls risk in this population. The purposes of this study were to compare two measures of postural stability, sway excursion and virtual time-to-contact, with disease severity in persons with diabetic neuropathy in response to anteroposterior and mediolateral support-surface perturbations and to identify the relationship between virtual time-to-contact and disease severity in persons with diabetic neuropathy in response to oblique support-surface perturbations. We hypothesized that virtual time-to-contact would provide a more sensitive and robust measure of postural stability for people with diabetic neuropathy in response to anteroposterior and mediolateral perturbations. We also hypothesized that as disease severity increased, postural stability would decrease in response to oblique perturbations. We expected a direct relationship between disease severity and sway excursion and an inverse relationship between disease severity and virtual time-to-contact.

Postural kinematics and force plate data were collected for ten adults with diabetes and a range of neuropathy from none to moderate-severe. Postural kinematics were collected using an eight-camera Qualisys motion capture system. Perturbations were controlled by and force plate data was collected using a NeuroCom Research Module. Each participant was perturbed in eight directions, at two speeds per direction (10 cm/sec and 20 cm/sec), and for two trials for each

condition for a total of thirty two perturbations. Nine statistically significant correlations were found between disease severity and virtual time-to-contact, while one statistically significant correlation was found between disease severity and sway excursion. Interestingly, the nine correlations between disease severity and virtual time-to-contact were all positive correlations.

We had support for our first hypothesis in that virtual time-to-contact had more correlations with disease severity than sway excursion across anteroposterior and mediolateral perturbations at both perturbation speeds. Our second hypothesis was not supported, in that virtual time-to-contact increased in response to oblique perturbations as disease severity increased. On average, virtual time-to-contact can explain 58% of the variation in disease severity. Further research is needed into why virtual time-to-contact was unexpectedly directly correlated with disease severity of diabetic neuropathy.

Evaluating Two Measures of Postural Stability in Response to Perturbations in People with Diabetic Neuropathy

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By:

Matthew G. Becker

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By

Matthew G. Becker

APPROVED BY:

DIRECTOR OF THESIS: _____
Paul DeVita, PhD

COMMITTEE MEMBER: _____
Zachary Domire, PhD

COMMITTEE MEMBER: _____
Stacey Meardon, PhD

COMMITTEE MEMBER: _____
Sunghan Kim, PhD

CHAIR OF THE DEPARTMENT OF KINESIOLOGY: _____
Stacy Altman, JD

DEAN OF THE GRADUATE SCHOOL: _____
Paul J. Gemperline, PhD

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Chapter 1 – Introduction

Diabetes mellitus, commonly referred to as diabetes, affects approximately 25.8 million people in the United States, or roughly 8.3% of the national population [1]. Diabetes is characterized by malfunctions in the insulin system, either in insulin production or insulin action and it results in high blood sugar levels. Some problems with diabetes are hyperglycemia and blood sugar spikes, which often result in needing dietary adjustments and possible medication. One of the possible complications of diabetes is peripheral neuropathy, particularly in the lower limbs. Diabetic peripheral neuropathy is a marked decrease in proprioception, particularly in the lower body, as determined by sensitivity and nerve conduction velocity tests. It has been shown to cause delays in both sensory and motor neuron function [2-5] and these delays lead to musculoskeletal complications with maintaining balance and stability. These issues, in turn, lead to an increase in falls risk [6]. Falling can lead to injury, hospitalization, demobilization, and other complications.

People with diabetic peripheral neuropathy are much less stable while standing than people without this disease. They show a larger sway range in the anterior-posterior and medial-lateral directions and an increased mean sway velocity under quiet standing conditions [5,7,8]. The larger sway range, i.e. increased postural instability, occurs because neuropathic patients have a diminished ability to sense and correct minute changes in acceleration of their bodies. Therefore, they can sense and correct only larger changes in acceleration, which exist in larger ranges of sway. Because people with diabetic peripheral neuropathy have a diminished sensory and motor ability in the ankle joints, they use more of a hip strategy in order to balance themselves [9,10].

Postural stability is the maintenance of balance during quiet standing. It has traditionally

been determined by measuring changes in center of pressure or center of gravity while a person is standing on a force plate [7,8,10]. The center of pressure is the location of the net ground reaction force vector on the ground. The center of gravity is the vertical projection of the center of mass onto the ground [11]. During successful quiet standing, the position of the center of pressure, the point at which the floor reaction force is applied to the person, translates horizontally. In order for balance to be maintained, the center of pressure must stay however within the boundary of stability, an area defined by size and position of the feet. A larger magnitude in displacement of the center of pressure or a higher average displacement velocity has traditionally meant that a person is less stable [7,10]. A larger sway range is problematic because it indicates that a person is closer to being outside of their boundary of support before they can correct themselves. If the center of pressure moves outside of the support boundary, the person will lose balance and either has to catch him or herself or fall. Traditionally, models for quiet standing have resembled an inverted pendulum, with the body acting as relatively straight and uniform and rotating around or oscillating about the ankle joints, commonly referred to as an ankle strategy for maintaining postural control [9,10]. A hip strategy resembles a double inverted pendulum, rotating about both the hips and ankles to maintain stability, instead of acting as fixed body rotating about the ankles only. The hip strategy involves more biomechanical degrees of freedom, and higher degrees of freedom lead to decreased stability [12].

The ultimate goal of analyzing postural stability during quiet standing and in response to perturbations is to identify risks for and ideally prevent falling. Falling can result in injury, impairment and can ultimately lead to disability. Instabilities in posture can manifest themselves directly to increased risk of falling or indirectly through locomotion instabilities to increased risk

of falling. People with diabetes have been shown to be at an increased risk of falling, with people who have poorly controlled diabetes symptoms to be an even greater risk for falling [6,13].

Postural instabilities are assessed by investigating changes in the position of the center of pressure, the center of gravity, and changes in the ground reaction force. All of these are sound, reliable measures, but they lack the ability to describe the level of instability, as it pertains to predicting when a person might fall. They lack the context of an individual's base of support in their calculation. The base of support, also known as the boundary of stability, is the area in which the center of pressure can be supported, usually defined on the lateral borders by the width of a person's feet and defined on the anterior and posterior borders by the length of a person's foot from toes to heels. When the center of pressure is outside the base of support, a fall or corrective step is imminent. The majority of the research has been about a numerical value to represent stability where higher values are seemingly indicative of decreased postural stability, but with no concrete notion of how to apply that level of stability to falling. Measuring sway excursion with center of pressure has limited utility when a person is not using an ankle strategy to maintain stability. The measurement of sway is based on the assumption that a person is rotating about the ankles, with no other mobile joints [14]. Diabetics, both with and without peripheral neuropathy, use more of a hip strategy to maintain postural stability. This raises into question the validity of using these traditional and basic measures of sway when measuring neuropathic patients. A relatively new method called time-to-contact addresses both of these issues. Time-to-contact is a measure of how quickly a person's center of pressure will be outside the boundary of stability, based on the instantaneous horizontal position, velocity, and acceleration, and position of a person's center of pressure relative to the support boundary. It does not assume that an individual is oscillating around the ankles or any other single joint. The

balance strategy that a person uses is irrelevant to time-to-contact, because it simply only shows how quickly a person's center of pressure will be outside of their boundary of stability, if they do not alter their center of pressure location, regardless of balance strategy. Time-to-contact was shown to be a more sensitive measure of stability compared to traditional measures of sway, when used in populations with neurological disorders, such as concussed athletes [15], scoliosis patients [16], and multiple sclerosis patients [17]. It has potential to become a better measure of postural stability for populations that do not primarily use an ankle strategy during quiet standing.

Hypotheses

- Virtual time-to-contact will provide a more sensitive and robust measure of postural stability in predicting disease severity in people with diabetic neuropathy in response to anteroposterior and mediolateral translational perturbations.
- As disease severity increases, postural stability will decrease in response to oblique translational perturbations, as assessed by lower virtual time-to-contact.

Purposes

The purpose of this study is twofold. The first purpose of the study is to compare the relationships of time-to-contact and center-of-pressure sway area with disease severity in anteroposterior and mediolateral perturbations in people with diabetic neuropathy. The second purpose is to identify the relationship between neuropathic severity and postural stability measure time-to-contact during oblique postural perturbations.

Delimitations

- All participants will be diabetic, with some having diabetic peripheral neuropathy and others having diabetes but not neuropathy.
- Participants will be between the ages of 21 and 60 years old.
- Participants will have a BMI < 37.5 kg/m^2
- Participants will be excluded if they use a walking implement (cane, walker, etc) or cannot stand still unassisted for less than 30 seconds.
- Participants will be excluded if they have any cardiovascular or neurologic diseases (other than diabetic peripheral neuropathy).
- Participants will be excluded if they have a diabetic foot ulcer.

Limitations

- Information on people with higher severities of neuropathy cannot be collected due to them being unable to stand unassisted by a walking implement or them having other complicating medical conditions.
- Participants will be considered to have diabetic peripheral neuropathy if they are above the thresholds in either the vibration threshold test or the pressure threshold test.
- All interview information collected was assumed to be correct.

Chapter 2 – Literature Review

The first purpose of this study is to compare the relationships of postural stability measures time-to-contact and center-of-gravity sway area with disease severity in anteroposterior and mediolateral perturbations in people with diabetic neuropathy. The second purpose is to identify the relationships among neuropathic severity and duration with postural stability measure time-to-contact during oblique postural perturbations. This review of literature will focus on 1) Postural Control, 2) Diabetes Overview, 3) Diabetic Peripheral Neuropathy and 4) Measures of Postural Stability Assessment.

Postural Control

Introduction

Postural stability, also referred to as balance, is the ability to control the center of mass in relationship to the base of support [18]. In the human body, there are three primary postural control input mechanisms used during quiet standing for healthy populations. The three mechanisms are the vestibular, visual, and somatosensory afferents [19,20]. These three sensory mechanisms are thought to integrate with each other to maintain balance during quiet standing as well as during movement. This integration requires a certain degree of organization such that visual, vestibular, and somatosensory information from both sides of the body are compared and weighted for availability, accuracy, and task needs prior to and throughout action

Sensory Strategies

When one of these mechanisms is eliminated or degraded, the other two are usually sufficient or relied upon more heavily to maintain postural stability, after a short period of adjustment [21]. For example, when vision is eliminated from use, people can still maintain balance by using their vestibular and somatosensory afferents. However, when vision is made unavailable to healthy subjects (standing with eyes closed or standing in a dark room), postural sway area is significantly increased [7,10,22-24]. In contrast, some studies have shown that sway area does not significantly increase in healthy control subjects when vision is not available [9,13,25]. It should be noted that although sway area may or may not have increased in these studies, balance, defined as maintaining the position of the center of gravity within a base of support [26], was still maintained, despite vision being lost or compromised, as long as the two other primary inputs were still available.

The same compensatory paradigm holds true for either vestibular or somatosensory loss during both quiet and perturbed standing. When ischemia was induced at the level of the ankles and knees during perturbed bilateral standing, sway area of the center of pressure (COP) increased, with ischemia at the level of the thigh COP sway area was even greater with an associated increase in COP velocity [20]. This study shows that information from afferent muscle spindles and Golgi tendon organs above the level of ischemia provide enough feedback to maintain stability during sway-referenced perturbations in the sagittal plane at higher frequencies, but were not sufficient for stability with low frequency perturbations. However, vision was able to compensate for low frequency perturbations. Another study showed no significant increase in postural sway area with loss of somatosensory information from the feet and ankles [21]. In this study, ischemia above the level of the knees did result in increased sway in

quiet stance. However, more of a hip strategy (which will be discussed later in this review of literature) was used to maintain balance when somatosensory information from the legs and ankles was limited [21]. The loss of somatosensory information has been associated with an increase in vestibular sensitivity, suggestive of sensory re-weighting. This was also demonstrated in a study in which subjects with diabetic peripheral neuropathy stood quietly on a foam surface on top of a force platform while undergoing galvanic stimulation to induce anterior sway [27]. The galvanic stimulation had a greater effect on the movement of the trunk than on the movement of the body's center of mass. This study suggests that the vestibular system controls trunk orientation, not posture. Trunk orientation is an indirect way to control postural stability. During quiet standing, balance is still maintained, albeit some of the subjects exhibited signs of instability.

Postural Control Models

One of the major prevailing models of postural control during quiet standing is that the body acts as an inverted pendulum during swaying [11]. This inverted pendulum model is known as the ankle strategy [19,28]. In an ankle strategy, the body is considered a stiff, inflexible object that rotates about the ankles [19,29]. All corrective postural torques are generated from the muscles of the lower leg about the ankle joint [30]. This model is valid, primarily for small perturbations in the anteroposterior direction and when the surface of support is longer than the contact surface of the foot [19,29,31]. However, due to the short length of the foot in relation to the body, the ankle cannot produce large amounts of torque. Therefore, it is not the primary strategy used when the body needs to react quickly to large perturbations.

The hip strategy is the second strategy used in postural control during quiet standing. In opposition to the ankle strategy, the hip strategy is when the body is divided into two levers, rotating about two axes, the ankles and hips [19,28,30]. The hip strategy is used almost exclusively in mediolateral rotations [10], when the center of gravity is close to the boundary of stability [32], in response to large and fast anteroposterior perturbations, and during anteroposterior perturbations when the support surface is shorter than the contact surface of the foot [10,19,30]. In the mediolateral direction, the hips provide postural stability through the load-unload mechanism and through activation of the abductor and adductor hip muscles [29]. The load-unload mechanism is used primarily at the hip joint by unloading one side while simultaneously loading the other. This is primarily used to reverse postural sway to one side in the mediolateral direction. Because the hips can generate much greater torques than the ankles, it is ideally suited to be the primary engine to facilitate postural change to maintain stability when there is a large anteroposterior perturbation that the muscles of the ankle joint alone cannot handle or when the center of gravity is nearing the boundary of stability and requires a large torque to remain within the boundary.

Although these two distinct strategies exist for postural control during quiet standing, they are not exclusive. During any point in time, both strategies are being used [10,19,30]. Even in instances when the ankle strategy is not the primary strategy used to control stability, proprioceptors in the ankle are responsible for the initial postural responses to surface perturbations [21]. Their usage is continuum-based, exclusive ankle strategy on one end and exclusive hip strategy on the other end. However, the ends of the continuum are never reached. As an example of this continuum, the hips are responsible for about 90% of the postural stability in the mediolateral direction, but only contribute about 15-20% to postural stability in the anteroposterior direction in persons with diabetic neuropathy during quiet standing [10].

It has been demonstrated through usage of EMG during perturbations on persons with induced somatosensory loss that response time of postural muscles is the same, as compared to control subjects [21]. However, that same study found that muscles associated with the hip strategy (quadriceps and rectus abdominis) contracted with greater intensity. There were also higher intensity co-contractions in the hamstrings and lower back, which are the antagonist muscle groups to the quadriceps and rectus abdominis, respectively. When the body experiences somatosensory loss, it adopts a more conservative balance strategy with co-contraction of agonist and antagonist postural control muscle groups, and higher intensity contractions of postural control muscles around the hips.

Diabetes Overview

Diabetes mellitus, commonly known as diabetes, is a disease of insulin physiological defect or action. Over 25.8 million people are currently affected by diabetes in the United States alone (roughly 8.3% of the population) [1]. There are two types of diabetes, Type 1 (commonly referred to as insulin-dependent diabetes) and Type 2 (formerly known as adult-onset diabetes) [1]. Insulin is hormone that binds to and stores glucose in the liver or skeletal muscles. In Type 1 diabetes the body cannot produce insulin and patients must rely on synthetic insulin that is injected into the body on a daily basis. In Type 2 the body becomes insulin resistant to glucose and cannot produce enough insulin to absorb sufficient amounts of glucose, which ends up circulating in the blood stream. This extra glucose that circulates around the body en masse in the blood stream causes issues such as endothelial damage and can lead to nerve impulse issues which can lead to neuropathy. Patients with Type 2 diabetes rely on oral medication and a

controlled diet to manage their blood glucose levels. Type 2 diabetes accounts for 90-95% of the cases of diabetes in adults [1].

It is interesting to note that diabetes, even when controlled through diet, exercise, and medication, can cause issues with the vestibular system. Persons with diabetes who were subjected to cell counts of Scarpa's ganglion in the vestibular nerves showed up to a 55% loss in ganglion cells when compared to control subjects [33]. This is believed to be due to excess glucose in the blood stream, which can result in vascular insufficiencies in the arteries [33].

Diabetes does appear to result in possible decreased muscular capabilities. Some studies have shown that maximal muscular strength decreases as a result of having diabetes [34,35] and one study found decreased maximal muscular strength (20% less for ankle dorsiflexion, 21% less in ankle plantarflexion, 16% less in knee extension, and 17% less in knee flexion) in persons with diabetic peripheral neuropathy, but not persons with diabetes without peripheral neuropathy [36]. One study found that in addition to decreased maximal strength, persons with diabetes also had greater short-term muscular endurance, meaning that they saw less of a decline in torque production in knee flexion, knee extension, and ankle dorsiflexion, as tested on an isokinetic dynamometer, as compared to control subjects [35].

Won et al looked at muscle strength in persons with Type II diabetes and muscle quality was defined as maximal muscular strength divided by muscle mass [34]. Persons with diabetes had greater muscle mass than control subjects (9.1 kg vs 8.7 kg for men's legs, 3.6 kg vs 3.4 kg for men's forearms, 7.0 kg vs 6.3 kg for women's legs, and 2.3 kg vs 2.1 kg for women's forearms, all statistically significant differences), but lower maximal strength, and therefore had lower muscle quality (14.2 Nm/kg vs 15.3 Nm/kg for men's legs, 10.8 Nm/kg vs 11.7 Nm/kg for men's

forearms, 12.1 Nm/kg vs 13.0 Nm/kg for women's legs, and 11.0 Nm/kg vs 12.0 Nm/kg for women's forearms, all statistically significant differences). This could be explained by the suggestion that hyperinsulinemia may cause changes in muscle fiber distribution that result in a higher percentage of type IIb muscle fibers [37]. This study also found that men and women with type II diabetes had muscle morphologies that were very similar to obese women. These people with type II diabetes had a significantly lower percentage of type I muscle fibers and correspondingly, a significantly higher percentage of type II muscle fibers (especially type IIb fibers) and had less capillaries supplying blood-flow to both type I and II muscle fibers. These muscular morphology abnormalities are interesting in that muscle fiber composition has been linked with insulin sensitivity levels [38]. Specifically, type IIb fibers correlate well with higher levels of insulin resistance, one of the primary symptoms and issues with type II diabetes.

Persons with diabetes have also been shown to be unresponsive to perturbations with small accelerations [3]. They require quicker accelerations to detect movement of the support surface. Persons with peripheral neuropathy but no diabetes have been shown to require higher thresholds of ankle eversion and inversion movements to detect a change in in the rotational orientation of the support surface [4]. Taken together, these studies show that both diabetes and non-diabetic peripheral neuropathy cause a loss in proprioception of the lower limbs in response to small movements and accelerations. This means that smaller perturbations do not result in corrective postural responses in these populations, and thus increased chance of falling.

Persons with diabetes and/or peripheral neuropathy have been determined to have a higher risk of falling than healthy control subjects. In a retrospective questionnaire study, persons with diabetes and peripheral neuropathy were 55% more likely to fall than persons with diabetes and no neuropathy [6]. In a study looking at postural sway complexity and falls risk in

diabetics, diabetic non-fallers had similar physiological function score to healthy fallers, with diabetic fallers having worse scores than either of those groups or healthy non-fallers [13]. In older women who reported falling at least once in the past year, older women with diabetes were reported to have fallen more and diabetes was determined to be a risk factor in falling [39]. Older women with diabetes who were not using insulin for diabetic control had a 68% greater risk of falling more than once a year as compared to healthy controls. Older women with diabetes and using insulin had an almost 180% greater chance of falling as compared to healthy controls. Decreased vibratory and pressure sensitivity were also found to be risk factors for falling more than once in a year. This is of particular concern because those are two clinical tests for diabetic peripheral neuropathy.

Persons with peripheral neuropathy, both diabetic and non-diabetic, have been found to have higher rates of falling. Richardson et al. looked at non-diabetic persons with peripheral neuropathy and found that they were 5 and a half times more likely than healthy controls to fall [40]. In a study comparing persons with diabetes and peripheral neuropathy to persons with diabetes and no neuropathy, the persons with diabetes and peripheral neuropathy were 15 times more likely to suffer an injury from falling during walking[41].

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is a potential side effect of diabetes, particularly if blood glucose levels are not controlled well. DPN occurs in about 50% of people with long-standing diabetes [42]. It interferes with both afferent and efferent neurons, causing delays in action potential transmission. DPN is not completely understood, but it is believed to cause

these delays by destroying neural axons and not through demyelination of neurons [43]. In otherwise healthy individuals, neighboring neurons can reinnervate muscle fibers with neuronal loss, but this does not appear to be the case in DPN. Typical symptoms of DPN are loss of thermal sensitivity, loss of vibratory sensitivity, loss of pressure sensitivity, and depressed tendon reflexes [44,45].

Postural stability issues in diabetic and diabetic peripheral neuropathy patients are generally attributed to issues with the proprioceptive mechanisms of the lower limbs [7]. In patients with diabetic neuropathy, both afferent and efferent neurons and muscle fibers are impacted [2]. These nerve issues results in slower neural transmissions which lead to slower muscle responses. Muscle responses to perturbations are delayed in this population [46,47]. However, it is unknown exactly to what extent each type of neuron, afferent or efferent, is affected to cause these delays in muscle response.

People with DPN are significantly less stable than healthy control subjects or even persons with diabetes but no neuropathy symptoms [7-10,24,25,48-50]. In a study by Boucher et al., persons with DPN had a higher mean sway speed and a larger sway area [7]. In another study, mean sway velocity was higher in persons with DPN than in control subjects or subjects with diabetes but no neuropathy [9]. Horak et al, found that persons with DPN had more postural sway than control subjects during quiet standing on a firm surface with both eyes open and eyes closed [49]. LaFond et al. found that elderly persons with DPN had greater center of pressure displacement in both the sagittal and frontal planes, higher mean sway velocity, and larger sway area than healthy elderly subjects [10]. Simoneau et al., found that persons with DPN had a larger center of pressure sway range [48]. In a study that used accelerometers instead of force plates to detect postural stability issues, Persons with DPN were found to have higher sway ranges in the

sagittal plane for both the lumbar and ankle accelerometers [24]. Persons with DPN are also significantly less stable when balancing on one leg [51]. Interestingly, subjects with sub-clinical levels of diabetic peripheral neuropathy also have been shown to demonstrate balance deficits, as shown by using dynamic posturography [47].

Other studies have also had similar findings during quiet standing. Using accelerometers, Turcot et al found that people with diabetic neuropathy had a higher range of sway and greater range of AP lumbar acceleration compared to diabetics without neuropathy and healthy controls[24]. LaFond et al found that people with diabetic neuropathy had a larger sway area, higher sway velocity, and larger COP range of sway in the AP and ML planes compared with healthy control.[10]. Ahmmed et al looked at sway during quiet standing with eyes open and eyes closed found that people with diabetic neuropathy had a higher AP sway range with eyes open and eyes closed and a higher ML sway range with eyes closed compared to diabetics with no neuropathy and healthy controls[50]. Yamamoto et al found that people with diabetic neuropathy had greater sway area and higher sway velocity than people with diabetes and healthy controls[8]. This study also found that people with diabetes were not different from healthy controls in any of the postural measures. Giacomini et al found that people with diabetic neuropathy had increased center of gravity mean sway velocity compared to people with diabetes and no neuropathy and healthy controls (12.08 mm/sec vs 7.6 mm/sec and 4.65 mm/sec, respectively)[9]. Nardone et al found that people with diabetic neuropathy had a greater COP sway area than healthy controls[25]. These studies all serve to paint a picture that people with diabetic neuropathy have postural stability deficits during quiet standing as compared to healthy controls and people with diabetes and no neuropathy. Based on quiet standing, we would expect people with diabetic neuropathy

to have low VTC, with greater disease severity equating to lower VTC based on the higher sway velocity.

In order to measure diabetic peripheral neuropathy clinically, there are three major tests. The first test is a nerve velocity conduction test [44,45]. This is performed on the distal extremities, usually of the lower limbs. An electric current is applied to motor and sensory nerves and the rate of transmission is measured distally in the extremity. The second test uses a biothesiometer, which is an instrument that applies vibrations at a set frequency to a testing site on the body, usually on the plantar surface of the foot [52]. The frequency remains the same throughout the test, but the voltage increases to intensify the frequency. A person with diabetes is considered neuropathic if they can't feel any vibrations below the 25V threshold. An alternative to using a biothesiometer is to use a series of tuning forks in a similar manner. The third test is the Semmes-Weinstein multifilament test [53]. This test uses monofilament wires of differing thickness to check for sensitivity, usually on the patient's feet or hands. A diabetic person who cannot feel anything thinner than the 5.07g monofilament is considered to have neuropathy. For the biothesiometer and Semmes-Weinstein tests, the above thresholds are thresholds for loss of protective sensation. This loss of protective sensation is considered to be due to neuropathy, thus the person would be considered to have neuropathy if they cannot feel vibrations below 25V or a monofilament smaller than 5.07g.

Measures of Postural Stability Assessment

Postural stability is the ability of the body to maintain balance. Various techniques are used to assess postural stability. Traditional measures include measuring changes in the

horizontal ground force vector, center of mass, center of gravity, and center of pressure [11]. Variables of interest often include position, velocity, direction, area and/or magnitude. Changes in horizontal ground reaction force are proportional to center of gravity acceleration [54]. The center of mass is a virtual point, usually within the human body in the abdominal or thoracic region when standing erect. The center of mass and the center of gravity are related in that the center of gravity is the vertical projection on the ground of the center of mass. The center of pressure is the location on the ground of the vertical ground reaction force vector. Balance is maintained by manipulating the position of center of pressure and ground reaction force to modulate the position of the center of mass. The center of pressure is a measurement taken directly from a force plate, while the center of mass and center of gravity have to be calculated using force and anthropometric data. Therefore, the center of pressure has much less inherent error.

In these traditional measures of postural stability, large increases in sway area or a higher mean sway velocity is general presumed to be indicative of greater postural instability [7,10,55]. These traditional measures of postural sway all operate under the paradigm that posture is maintained via referencing a stability point within the equilibrium range of the boundary of stability [28]. Traditional sway measures also operate under the assumption that only the ankle strategy is being used.

A limitation of the majority of postural control and balance studies that involve perturbations is that they use only perturbations in the sagittal or frontal planes [3,19,25,30]. This same limitation is also seen in studies that use sway-referencing techniques that rotate a platform in the sagittal plane about a mediolateral axis in response to a person standing on it [19,31,56]. This limitation can be understood and can potentially even be deemed a delimitation in the case of the

sway-referencing. This is because rotating a platform in the sagittal plane about a mediolateral axis allows the ankle malleoli to remain on the same transverse plane. This removes the possibility of inversion and eversion being the primary ankle movements. Inversion and eversion ankle moments are rarely major factors in quiet standing because any large adjustments in frontal plane posture are handled using the hip strategy.

A relatively new measure of postural stability called virtual time-to-contact (VTC) which calculates how long it would take a person's center of pressure to contact the boundary of stability, as defined by the outer boundaries of the feet [12,28]. It takes into account both instantaneous velocity and acceleration of the COP to calculate a virtual trajectory of the COP at each COP position. The virtual time-to-contact is how long it would take the virtual trajectory of each COP position to contact the boundary of stability. A higher VTC indicates a higher level of stability[12]. VTC uses a different paradigm in that stability is created and maintained by the body by adjusting the center of pressure so it remains safely within the boundary of stability [28]. Adjustments are made accordingly as the center of pressure approaches the boundary. If the center of pressure contacts the boundary, it results in a fall or a corrective action, such as taking a step. The center of pressure cannot exist outside of the boundary of stability, as the boundary is defined by the outline of the feet.

Because VTC relies on the center of pressure, and not the center of gravity, it does not rely on the person acting like an inverted pendulum. In clinical populations that rely primarily on mixed ankle and hip strategies or healthy populations in situations that utilize mixed ankle and hip strategies, VTC shows potential for being a more sensitive measure of postural stability. Another reason why VTC could be a more sensitive measure of postural stability is that it incorporates acceleration into the calculations [55]. A typical pattern observed in VTC studies is

that VTC actually increases as the center of pressure nears the boundary of stability, when balance is maintained [12,16]. VTC increases as the center of pressure nears the boundary of stability because the velocity and acceleration vectors are pointing towards the opposite side of the boundary. It has been used in concussed athletes to show that even when the athletes were asymptomatic and showed no deficits in traditional center of pressure sway measures, they still exhibited underlying balance problems which are indicative of residual postural control abnormalities [15]. VTC has also been used in children with scoliosis to detect deficits in the sagittal plane that were not detected using center of pressure sway [16]. VTC has also been proven to be a reliable measure of postural stability, with ICCs of .53 to .97 [57].

Virtual Time-to-Contact and the Assessment of Other Neurological Disorders

Neurological conditions other than neuropathy have been identified and/or categorized using a force plate and/or VTC. Chung et al found that dyskinesia in people with Parkinson's disease can be quantitatively assessed using a force plate[58]. They found that during quiet standing, the velocity of the center of pressure in AP plane was indicative of dyskinesia severity. Gruber et al found that center of pressure position parameters were not sufficient to assess postural control in adolescents with scoliosis[16]. Her research group used the more complex postural control measures of VTC and multiscale entropy. They found that adolescents with scoliosis had lower average VTC during quiet standing than healthy controls in the AP plane (93 ms compared to 120 ms). There were no differences in VTC between groups during quiet standing in ML plane (126 ms for scoliosis group vs 155 ms for control group). Cattaneo et al investigated differences between people with multiple sclerosis and healthy controls, participants

with multiple sclerosis had lower average VTC [17]. Slobounov et al reported no differences in COP measures between concussed athletes and healthy controls, with increases in VTC seen in concussed athletes[12]. Time-to-contact has been shown to be able to distinguish between healthy people and neurological disorder groups.

Summary

In summary, postural control is determined by visual, vestibular, and somatosensory afferents. Loss of one of these input mechanisms can result in the other two mechanisms covering up the loss in most conditions. Diabetes affects the somatosensory afferents. When exposed to differing visual and vestibular conditions, people with diabetes and especially with diabetic peripheral neuropathy show signs of decreased postural stability during quiet standing and recovery from short perturbations. The severity of neuropathy is related to decreases in static postural stability. Diabetic peripheral neuropathy has been shown to greatly increase falls risk, especially in older people. However, traditional measures of sway may not be the best measures to calculate postural instability in this population, due to their lack of reliance on the ankle strategy. Time-to-contact has been shown to be effective in identifying people with neurological disorders and may be a more sensitive measure to measure postural control in people with diabetes and diabetic peripheral neuropathy.

Chapter 3 – Methods

This study included an experiment to test the hypotheses that time-to-contact will provide a more sensitive and robust measure of postural stability and that as the severity of neuropathy increases, postural stability in oblique translations will decrease. This chapter describes the methods by which these hypotheses were tested. This chapter is divided into the following sections: 1) Subject Characteristics and Recruitment, 2) Instruments, 3) Protocol, 4) Data Regression, and 5) Statistical Analysis.

Participant Characteristics and Recruitment

Participants were recruited from Greenville, NC and surrounding areas. Recruitment was done via ECU mass email, newspaper advertisement, and fliers posted at the Diabetes Clinical Research Center at East Carolina University. Prior to the visit to the lab, interested volunteers underwent a brief interview questionnaire to determine eligibility for the study. Upon successful completion of the questionnaire, they were scheduled for one visit to the lab. Prior to participation in this study, all participants were provided to read and sign the East Carolina University IRB-approved informed consent. Ten participants were selected based on the following exclusion and inclusion criteria:

Exclusion Criteria:

- BMI > 37.5 kg/m^2
- Cardiovascular disease
- Neurological disease (other than diabetic peripheral neuropathy)

- Orthopedic surgeries/constraints
- Current smoker or recent history of smoking
- Any degenerative eye condition such as glaucoma, cataracts, or blindness
- Blood pressure > 160/90 mmHg

Inclusion Criteria:

- Adults between 20 and 60 years old with diabetes that can stand upright without assistance for up to 30 minutes at a time
- BMI < 37.5 kg/m^2

Instruments

Perturbations were controlled by the NeuroCom Research Module (Natus Medical Inc., Clackamas, OR) in order to assess postural responses. The NeuroCom Research Module gave center of pressure data from these postural responses. Postural kinematics were assessed using a bilateral, full-body reflective marker set, motion capture cameras, and motion capture software (Qualisys, Gothenburg, Sweden). Diabetic neuropathy severity was assessed using a Biothesiometer (Bio-Medical Instrument Co., Newbury, OH) and Semmes-Weinstein monofilaments (North Coast Medical, Inc. Morgan Hill, CA). For this study, a participant was considered to have clinical levels of neuropathy if they could not register a Biothesiometer vibration voltage of less than 25V at any of the five testing sites and/or they cannot register a monofilament smaller than 5.07 g.

Protocol

Upon entering the lab, participants had their height and weight measured, without shoes, on a stadiometer. Blood pressure was measured using a manual sphygmomanometer. Participants completed the following: an initial health survey, SF-36 v2 questionnaire, Short Physical Performance Battery (SPPB) test, 10-meter walk test, and the Timed-Up-and-Go test. They then underwent sensory threshold testing for neuropathy.

Subjects were positioned face down on a padded table with both feet supported and elevated so the feet faced upward for vibration and sensation threshold testing. Semmes-Weinstein monofilament testing occurred at five sites on the plantar surface of both left and right feet: the 1st toe, the 1st, 3rd, and 5th metatarsal heads, and the heel. Testing sites were randomized between subjects, but not between trials. Semmes-Weinstein testing followed the "yes-no" protocol, with participants being asked to respond when/where they felt the monofilament[59]. Participants were asked to say where they felt the monofilament to ensure that they were feeling it at the correct testing site. Participants were tested from smallest to largest monofilament. Monofilament sized increased until the monofilament could be felt at each testing site. From monofilaments 1.65 to 4.31, participants went through three trials at each site. For monofilaments 4.56 and above, participants only went through one trial at each site. If participants could feel a monofilament, testing at that site stopped and was recorded as the pressure threshold.

For Biothesiometer testing, the same five testing sites were used. The tip of the Biothesiometer was applied to the skin site, with minimal pressure. The voltage started at 0 V and was slowly increased until the participant registered the vibration. Subjects went through three trials of testing at each site.

After sensory threshold testing, participants had reflective markers placed on them, as described here: posterior superior iliac spine, anterior iliac spine, iliac crest, greater trochanter of the femur, lateral and medial aspects of the knee, lateral and medial malleoli of the ankle, posterior and lateral heel, 1^{st} and 5^{th} metatarsal heads, big toe, acromion process of the shoulder; and four-marker plates on the upper and lower legs.

After placement of all reflective markers was completed, the participants were secured to an overhead bar via an upper body safety harness to prevent falling. The participants then stood on the NeuroCom Research Module. They underwent thirty two total perturbations. They were perturbed in eight different directions (anterior, posterior, left, right, and at 45^{o} oblique angles), at two different speeds per direction (10 cm/s and 20 cm/s), and two trials for each speed. Each trial consisted of a half second of quiet standing, a half second-long perturbation, and five seconds of recovery. Force plate data was collected for postural responses the whole five and a half second trial. Any perturbations that resulted in the participant falling or having to take a step to maintain balance were repeated up to two more times, and if they still could not keep their feet in the same position, that perturbation was excluded from data analysis.

Data Reduction

All motion capture data was recorded and processed in Qualisys software (Qualisys, Gothenburg, Sweden). Time-to-contact was calculated using MATLAB software (MathWorks, Natick, Massachusetts). Center of pressure was measured by the NeuroCom Research Module and was used to calculate time-to-contact and AP and ML sway excursion. Time-to-contact was calculated for the instantaneous position vector on a five second virtual trajectory for each instant in time based on the instantaneous center of pressure, velocity, and acceleration. Time-to-

contact was calculated for each linear border of the stability boundary and the border with the smallest time-to-contact was considered the true time-to-contact of that point. The points used to create the boundary of stability were the reflective marker coordinates for the left and right big toe, 5th metatarsal head, and heel (Figure 1). The force platform and the motion capture system used different coordinate systems. During a perturbation trial, the foot markers moved in the motion capture coordinate system, but not in the NeuroCom coordinate system. Because the markers did not move relative to the force platform during a successful perturbation trial, only the first data point of the marker positions was used to create the boundary of stability for each trial. Center of pressure was used to calculate sway excursion. Center of pressure position data was filtered using a low-pass filter at 20 Hz. This filtered position data was differentiated once for velocity data and differentiated a second time for acceleration data. AP and ML sway excursion were calculated using the maximum and minimum AP and ML positions (respectively) of the center of pressure for the respective perturbation. AP sway excursion was only calculated for AP perturbations and ML sway excursion was only calculated for ML perturbations.

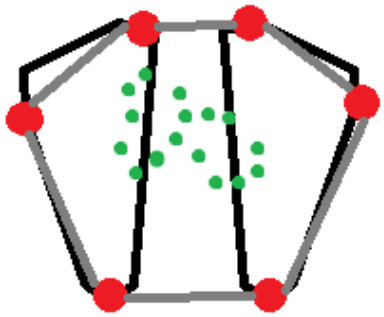

Figure 1. Conceptual virtual time-to-contact diagram. The feet are outlined in black. The boundary of stability is the gray line outlining the feet. Red dots indicate location of reflective markers placed on the feet (left and right big toes, 5th metatarsal heads, and heels). Note that the boundary of stability does not completely encompass the feet, with the anterior parts of the lateral toes not being included within the boundary of stability. This is due to reflective marker placement.

Statistical Analysis

All statistical analyses were conducted in MATLAB. Average and minimum time-to-contact during the perturbation and during the first second recovery period following the perturbation for all perturbation directions were regressed with both the left and right Biothesiometer voltage and Semmes-Weinstein monofilament score. A VTC graph for a sample perturbation trial is shown below (Figure 2). The Biothesiometer and the Semmes-Weinstein monofilament tests are both clinical tests. The Biothesiometer uses a clinical threshold of 25 V for loss of protective vibratory sensation[60]. The 5.07g Semmes-Weinstein monofilament is used as a clinical threshold for loss of protective pressure senstation[61]. The loss of protective sensation is considered to be due to neuropathy. AP and ML sway excursion were also regressed with left and right Biothesiometer voltage and Semmes-Weinstein monofilament score. Whichever method of assessing postural stability has a larger magnitude regression *r* value will be considered the better method of assessing diabetic neuropathy. The significance level for all statistical tests will be set *a priori* at $p < .05$.

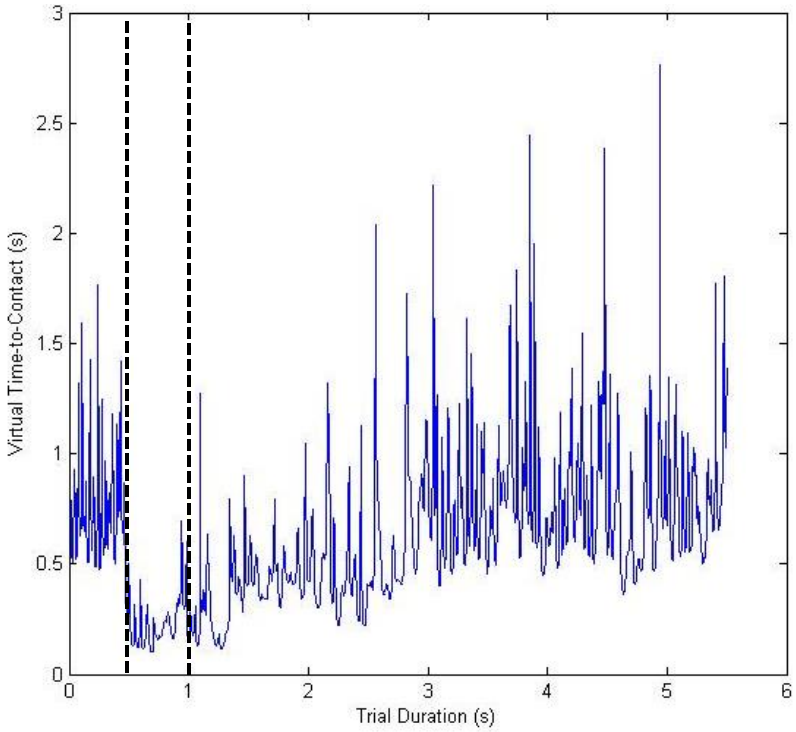

Figure 2. Virtual Time-to-Contact during a backwards perturbation trial at 20 cm/sec. The first .5 s are quiet standing. The first black dashed line is when the perturbation occurs at 0.5 s. The second black dashed line is when the perturbation ends and the recovery period starts at 1.0 s.

Chapter 4 – Results

It was hypothesized that time-to-contact (VTC) will provide a more sensitive measure of postural stability for people with diabetic neuropathy, in regards to anteroposterior (AP) and mediolateral (ML) translation perturbations. It was also hypothesized that as the severity of diabetic neuropathy increased, postural stability in response to diagonal translational perturbations will decrease. The purposes of this study were to compare the relationships of time-to-contact and center-of-pressure sway area with disease severity in anteroposterior and mediolateral perturbations in people with diabetic neuropathy and to identify the relationship between neuropathic severity and VTC during diagonal translational perturbations. This chapter is separated into the following sections: 1) Demographics, 2) AP Perturbations, 3) ML Perturbations, 4) Diagonal Perturbations, and 5) Summary.

Demographics

This study used 10 participants, 5 with diabetes and no diabetic neuropathy and 5 with diabetic neuropathy. Participant data by demographic is presented below (Table 1).

Table 1. Participant Data

	Age (years)	Height (m)	Mass (kg)	BMI	HbA_{1C} (%)
Diabetic without neuropathy	51.3 (7.14)	1.64 (0.07)	87.09 (8.88)	32.44 (3.97)	7.10 (1.65)
Diabetic with neuropathy	48.0 (13.42)	1.70 (0.13)	95.54 (16.82)	32.94 (5.72)	7.48 (2.50)

The vibratory threshold for each participant is presented below (Table 2). The vibratory threshold for each foot is an average of the vibratory threshold at the 5 plantar sites. Neuropathy severity was determined by using the foot with the highest vibratory threshold, as this represented the higher fall risk for each participant. It is interesting to note that each participant has a different vibratory threshold on each foot. This speaks to the variability of the effects of diabetes and neuropathy.

The Semmes-Weinstein scores for each participant are not provided in this document. No significant correlations were found between them and either VTC or sway excursion ($p < 0.05$).

Table 2. Vibratory threshold of both feet for each participant. The foot with highest vibratory threshold was determined to be their neuropathy severity.

	Left Foot	Right Foot
S01	3.73[a]	1.93
S02	3.80[a]	3.73
S03	10.42	26.20[a]
S04	8.73[a]	5.27
S05	13.07	32.40[a]
S06	8.87[a]	8.33
S07	10.00	17.87[a]
S08	4.60	6.33[a]
S09	12.53	24.20[a]
S10	8.20[a]	5.33

[a]Foot with highest vibratory threshold.

The number of incomplete perturbation trials is presented below (Figure 3). All perturbations trials at 10 cm/sec were completed. All perturbation trials at 20 cm/sec in the ML plane were completed. The perturbation directions are abbreviated as follows: F = front, FR = front-right, R = right, BR = back-right, B = backwards, BL = back-left, L = left, FL = front-left.

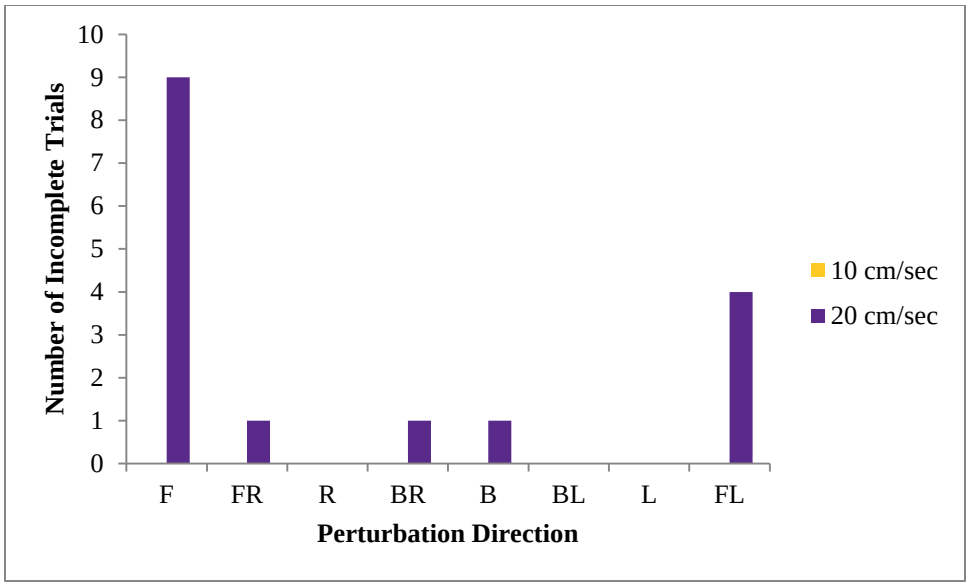

Figure 3. The number of incomplete perturbation trials by perturbation direction and speed. All perturbation trials at 10 cm/sec were completed.

AP Perturbations

AP perturbations contain results from both forward and back perturbations. Results from forward and backward perturbations were not significantly different between directions at each speed, but were different between speeds for each direction ($p < 0.05$). The correlation coefficients for AP perturbations are presented below for both average and minimum virtual time-to-contact and AP sway excursion during and after perturbations at 10 and 20 cm/sec (Table 3). Each variable (average VTC, minimum VTC, and AP sway excursion) was correlated with neuropathy severity. Significant correlations were found for average VTC during perturbations at 10 cm/sec ($r = 0.72$, $p < 0.05$) and average VTC during perturbations at 20 cm/sec ($r = 0.64$, $p < 0.05$). No significant correlations were found after perturbations at either perturbation speed. No significant correlations were found at either perturbation speed. It is interesting to note that both significant correlations were positive in direction meaning that VTC increased with disease severity.

Five of the ten participants could not complete at least one of the forward perturbations at 20 cm/sec, with eight total forward perturbations being unable to be completed. One participant could not complete one backward perturbation at 20 cm/sec. All other AP perturbation trials were completed. Trials unable to be completed were excluded from data analysis.

Table 3. Correlation coefficients for during and after AP perturbations. Average and Minimum are average and minimum time-to-contact.

AP Perturbations	10 cm/sec	During	Average	0.72*
			Minimum	0.22
		After	Average	0.23
			Minimum	-0.09
		Sway Excursion	During	-0.53
			After	0.49
	20 cm/sec	During	Average	0.64*
			Minimum	0.56
		After	Average	0.37
			Minimum	0.52
		Sway Excursion	During	-0.05
			After	-0.03

*Statistically significant, $p < 0.05$.

The relationships between average and minimum VTC and vibration threshold during (Figure 4A) and after (Figure 4B) AP perturbations at 10 cm/sec are shown below. A significant relationship was found between average VTC and vibration threshold during AP perturbations at 10 cm/sec ($r = 0.72$, $p < 0.05$). No other significant relationships were found.

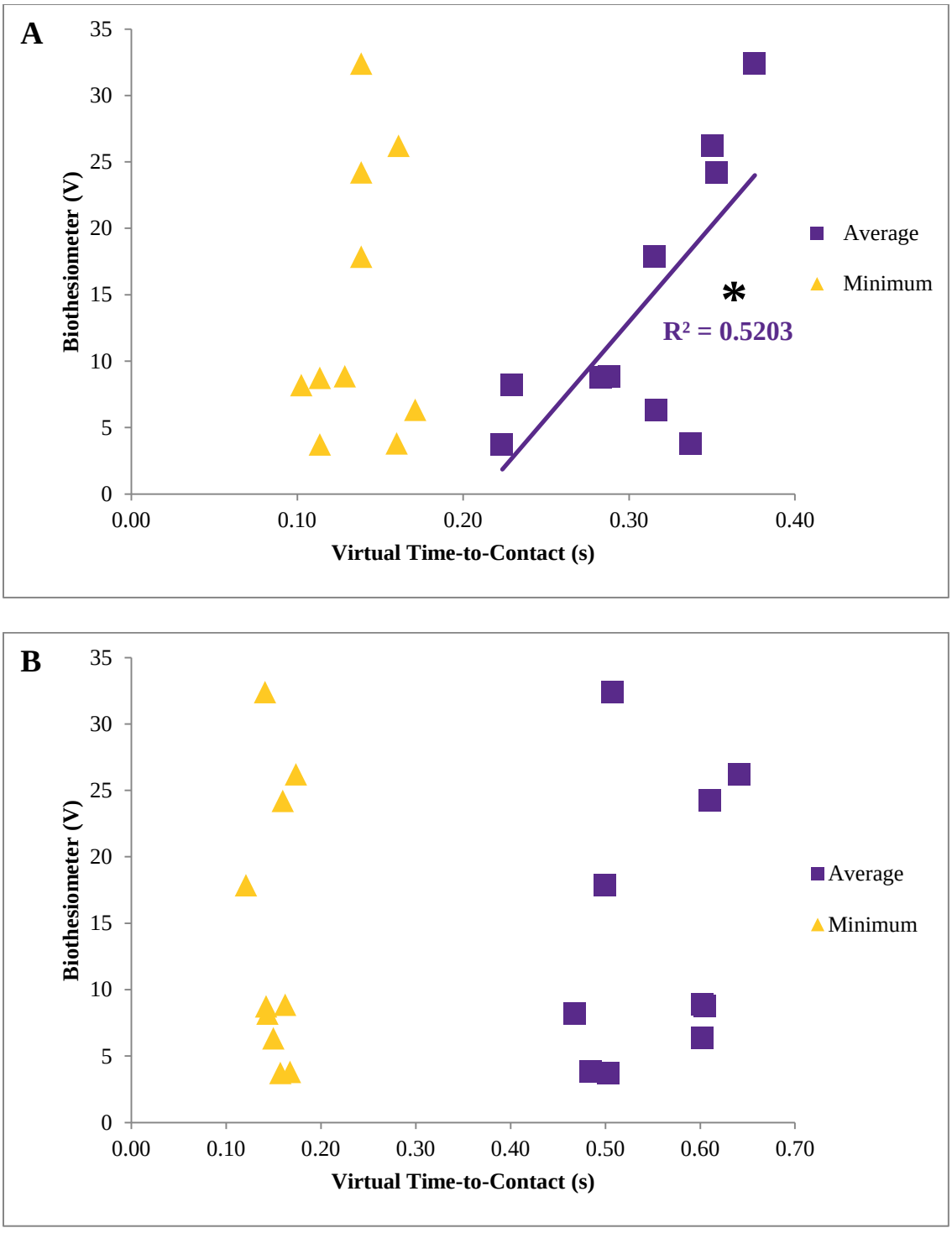

Figure 4. **A.** Average and minimum VTC versus vibratory threshold during AP perturbations at 10 cm/sec. **B**. Average and minimum virtual VTC versus vibratory threshold after AP perturbations at 10 cm/sec. * Statistically significant, $p < 0.05$.

The relationships between AP sway excursion and vibratory threshold during and after AP perturbations at 10 cm/sec are shown below (Figure 5). No significant relationships were found.

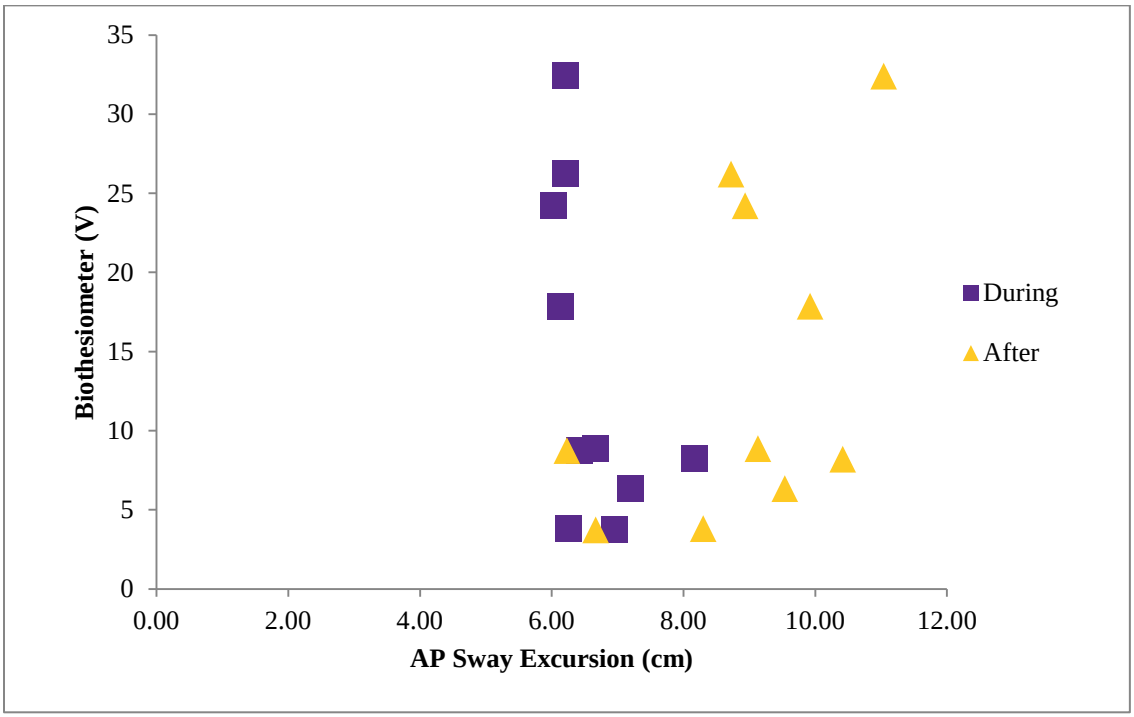

Figure 5. AP sway excursion during and after AP perturbations at 10 cm/sec. No statistically significant relationships were found, $p < 0.05$.

The relationships between average and minimum VTC and vibration threshold during (Figure 6A) and after (Figure 6B) AP perturbations at 20 cm/sec are shown below. A significant relationship was found between average VTC and vibration threshold during AP perturbations at 20 cm/sec ($r = 0.64$, $p < 0.05$). No other significant relationships were found.

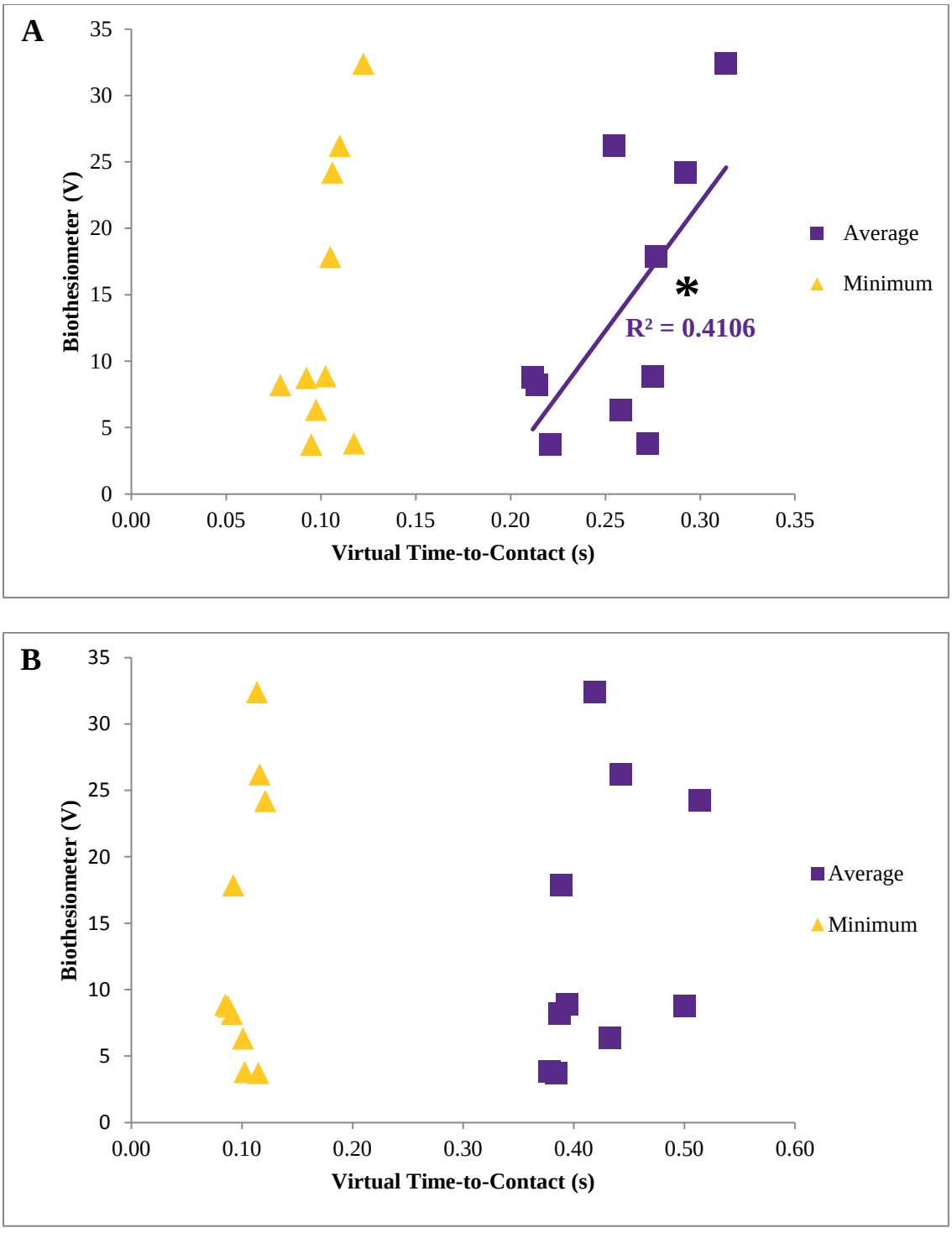

Figure 6. **A.** Average and minimum VTC versus vibratory threshold during AP perturbations at 20 cm/sec. **B**. Average and minimum virtual VTC versus vibratory threshold after AP perturbations at 20 cm/sec. * Statistically significant, $p < 0.05$.

The relationships between AP sway excursion and vibratory threshold during and after AP perturbations at 20 cm/sec are shown below (Figure 7). No significant relationships were found.

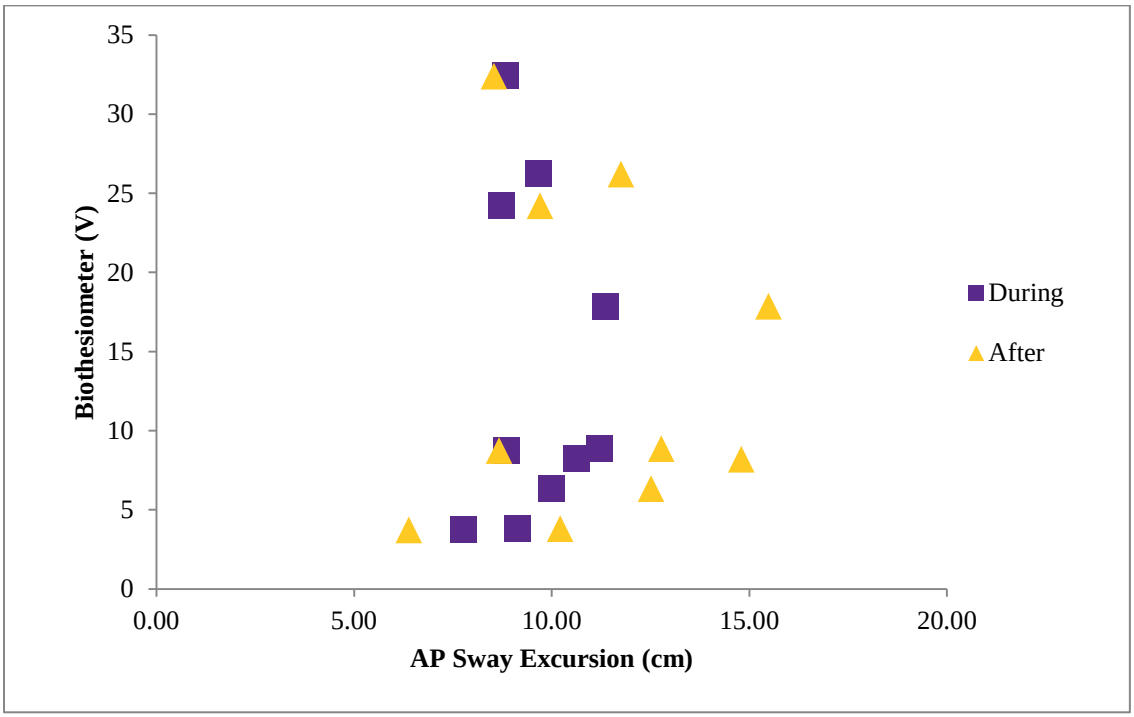

Figure 7. AP sway excursion during and after AP perturbations at 20 cm/sec. No statistically significant relationships were found, $p < 0.05$.

The average and minimum VTC with standard deviation error bars during and after AP perturbations at 10 cm/sec are shown below for the reader's information (Figure 8).

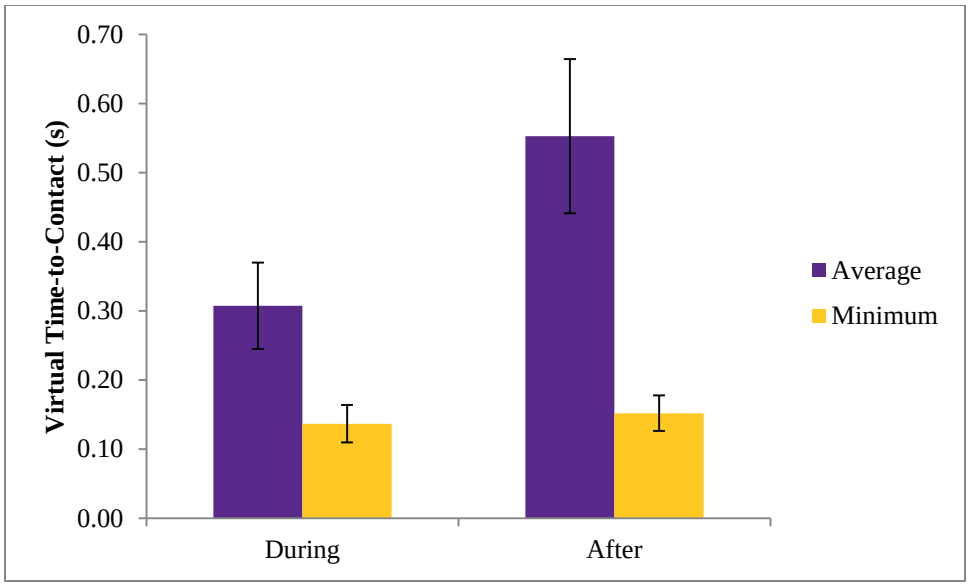

Figure 8. Average and minimum VTC during and after AP perturbations at 10 cm/sec.

The average and minimum VTC with standard deviation error bars during and after AP perturbations at 20 cm/sec are shown below for the reader's information (Figure 9).

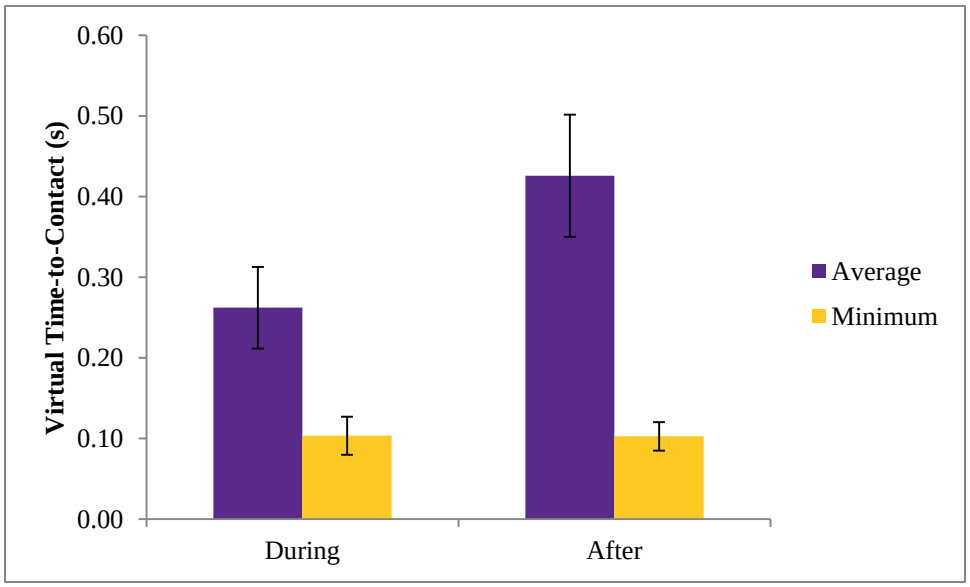

Figure 9. Average and minimum VTC during and after AP perturbations at 20 cm/sec.

AP sway excursion at 10 cm/sec and 20 cm/sec with standard deviation error bars during and after AP perturbations are shown below for the reader's information (Figure 10).

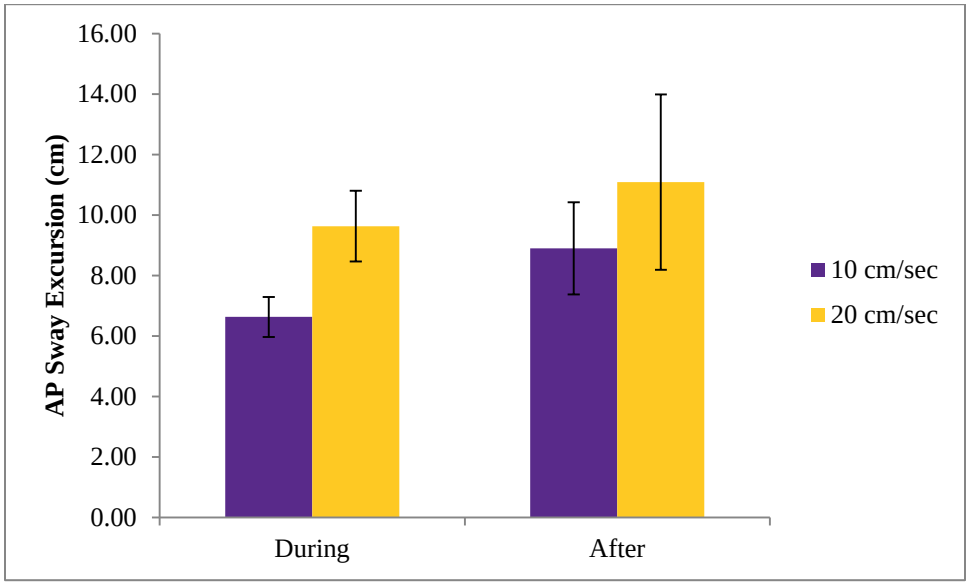

Figure 10. AP sway excursion during and after AP perturbations at 10 cm/sec and 20 cm/sec.

ML Perturbations

ML perturbations contain results from both forward and back perturbations. Results from left and right perturbations were not significantly different between directions at each speed, but were different between speeds for each direction ($p < 0.05$). The correlation coefficients for ML perturbations are presented below for both average and minimum virtual time-to-contact and ML sway excursion during and after perturbations at 10 and 20 cm/sec (Table 4). Each variable (average VTC, minimum VTC, and AP sway excursion) was correlated with neuropathy severity. Significant correlations were found for average and minimum VTC during perturbations at 10 cm/sec ($r = 0.66$ and 0.70, respectively), minimum VTC during perturbations at 20 cm/sec ($r = 0.83$), and ML sway excursion during perturbations at 20 cm/sec ($r = -0.67$), all $p < 0.05$. No significant correlations were found after perturbations at either perturbation speed or for sway excursion. It is interesting to note that as in AP perturbations, all significant VTC

correlations had a positive relationship again indicating increased VTC with increased disease severity.

All ML perturbation trials at both speeds were completed for all ten participants.

Table 4. Correlation coefficients for during and after ML perturbations. Average and Minimum are average and minimum time-to-contact.

ML Perturbations	10 cm/sec	During	Average	0.66*
			Minimum	0.70*
		After	Average	0.61
			Minimum	0.26
		Sway Excursion	During	-0.44
			After	-0.19
	20 cm/sec	During	Average	0.57
			Minimum	0.83*
		After	Average	0.38
			Minimum	-0.30
		Sway Excursion	During	-0.67*
			After	-0.31

*Statistically significant, $p < 0.05$.

The relationships between average and minimum VTC and vibration threshold during (Figure 11A) and after (Figure 11B) ML perturbations at 10 cm/sec are shown below. Significant relationships were found between average VTC and vibration threshold and minimum VTC and vibration threshold during ML perturbations at 10 cm/sec ($r = 0.66$ and 0.70, respectively, $p < 0.05$). No significant relationships were found after ML perturbations at 10 cm/sec.

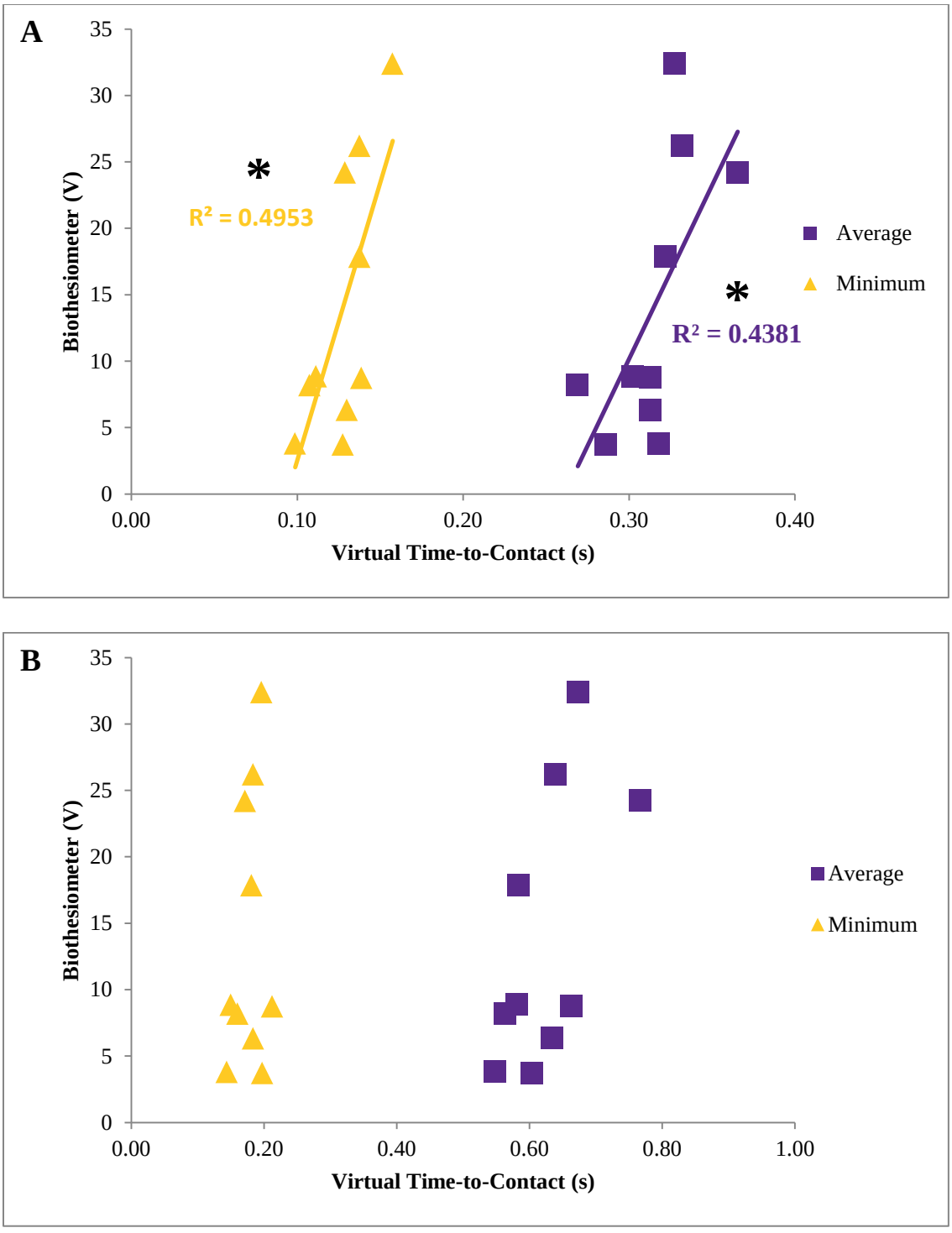

Figure 11. **A.** Average and minimum VTC versus vibratory threshold during ML perturbations at 10 cm/sec. **B**. Average and minimum virtual VTC versus vibratory threshold after ML perturbations at 10 cm/sec. * Statistically significant, $p < 0.05$.

The relationships between ML sway excursion and vibratory threshold during and after ML perturbations at 10 cm/sec are shown below (Figure 12). No significant relationships were found.

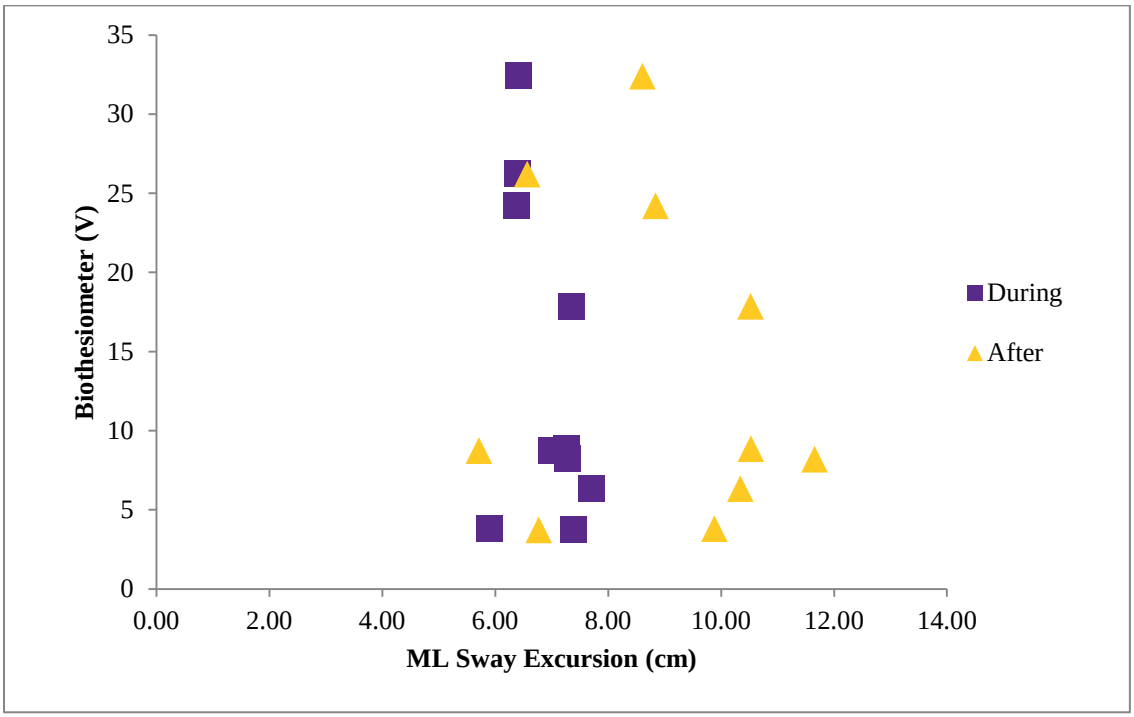

Figure 12. ML sway excursion during and after ML perturbations at 10 cm/sec. No statistically significant relationships were found, $p < 0.05$.

The relationships between average and minimum VTC and vibration threshold during (Figure 13A) and after (Figure 13B) ML perturbations at 20 cm/sec are shown below. A significant relationship was found between minimum VTC and vibration threshold during ML perturbations at 20 cm/sec ($r = 0.83$, $p < 0.05$). No significant relationships were found after ML perturbations at 20 cm/sec.

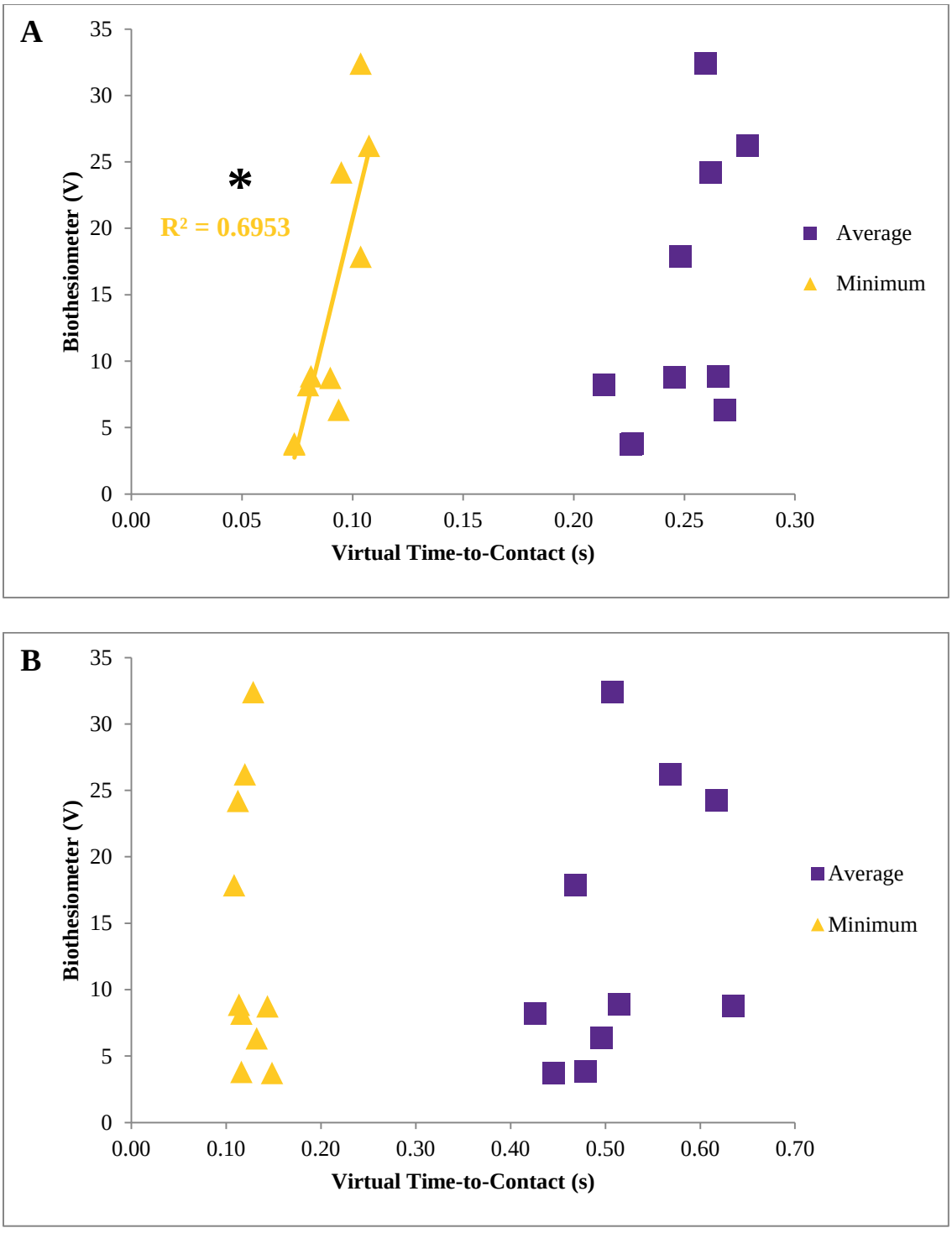

Figure 13. **A.** Average and minimum VTC versus vibratory threshold during ML perturbations at 20 cm/sec. **B**. Average and minimum virtual VTC versus vibratory threshold after ML perturbations at 20 cm/sec. * Statistically significant, $p < 0.05$.

The relationships between ML sway excursion and vibratory threshold during and after ML perturbations at 20 cm/sec are shown below (Figure 14). A significant relationship was found between ML sway excursion and vibratory threshold during (r = -0.67, $p<0.05$), but none was found after, ML perturbations at 20 cm/sec.

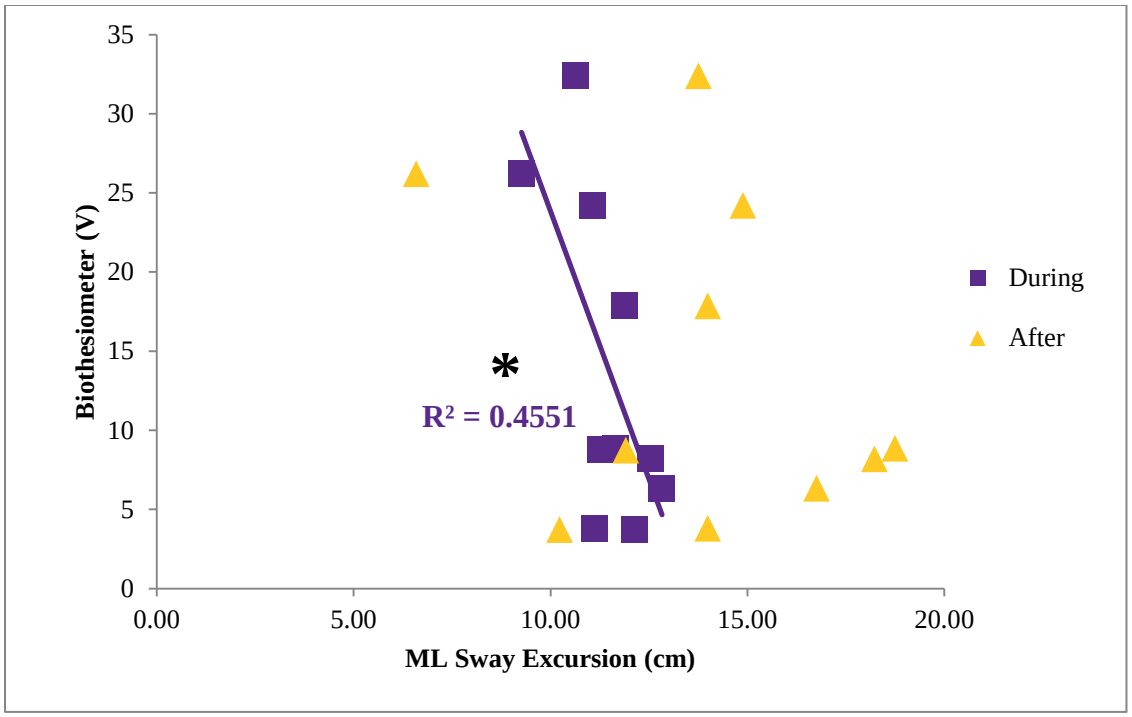

Figure 14. ML sway excursion during and after ML perturbations at 20 cm/sec. * Statistically significant, $p < 0.05$.

The average and minimum VTC with standard deviation error bars during and after ML perturbations at 10 cm/sec are shown below for the reader's information (Figure 15).

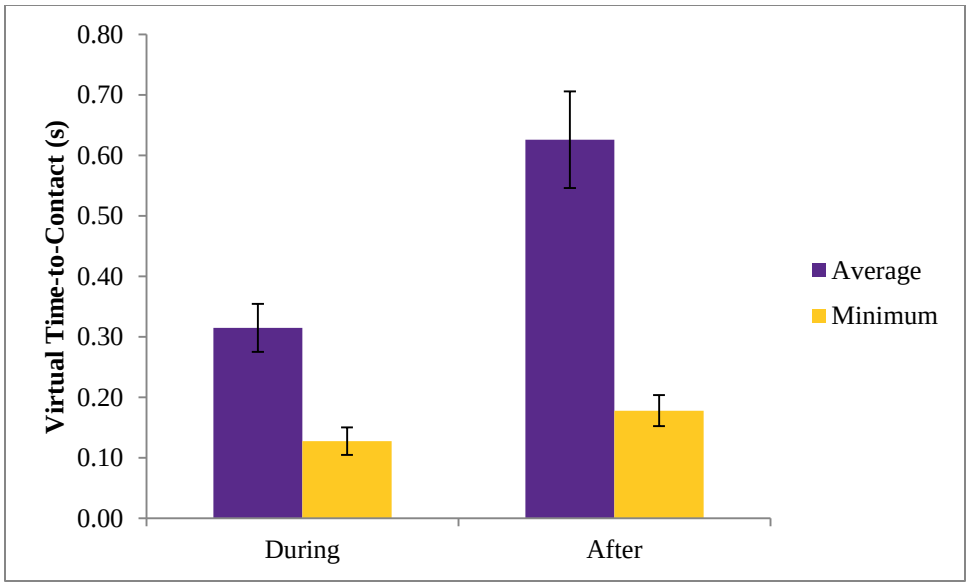

Figure 15. Average and minimum VTC during and after ML perturbations at 10 cm/sec.

The average and minimum VTC with standard deviation error bars during and after ML perturbations at 20 cm/sec are shown below for the reader's information (Figure 16).

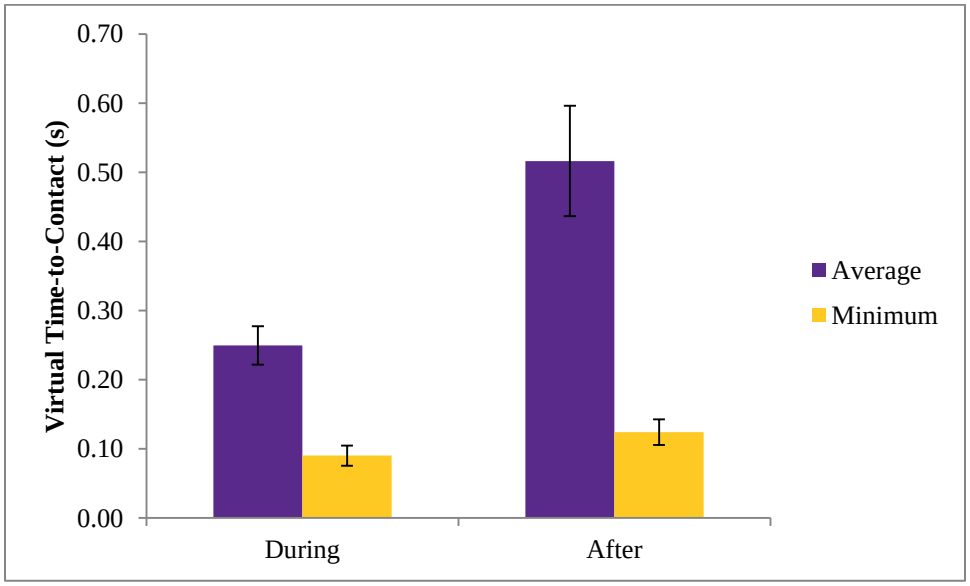

Figure 16. Average and minimum VTC during and after ML perturbations at 20 cm/sec.

ML sway excursion with standard deviation error bars at 10 cm/sec and 20 cm/sec during and after ML perturbations are shown below for the reader's information (Figure 17).

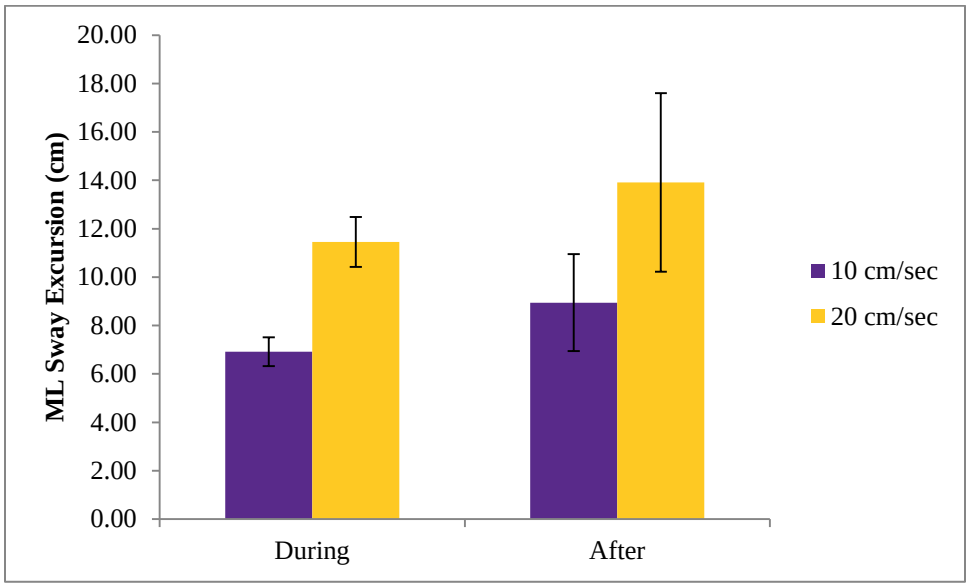

Figure 17. Sway excursion during and after ML perturbations at 10 cm/sec and 20 cm/sec.

A root mean square was calculated for the significant relationships involving VTC and both AP and ML perturbations. The root mean square was r = 0.71. When compared to the one significant correlation involving sway excursion, r = -0.67, it was apparent that VTC and sway excursion each predict ~45-50% of the variance in neuropathy severity across the significant relationships. However, VTC can predict this variance in five conditions, while sway excursion can predict this variance in only one condition. This speaks to the greater robustness of VTC as a predictor of neuropathy severity during and after AP and ML perturbations.

Diagonal Perturbations

The correlation coefficients for diagonal perturbations are presented below for both average and minimum virtual time-to-contact during and after perturbations at 10 and 20 cm/sec (Table 3). Both average VTC and minimum VTC were correlated with neuropathy severity. Significant correlations were found for average VTC and minimum during perturbations at 10 cm/sec (r = 0.86 for both) and minimum VTC during diagonal perturbations at 20 cm/sec (r = 0.79), all $p < 0.05$. No significant correlations were found after the perturbation at either perturbation speed.

Two of the ten participants could not complete at least one of the diagonal perturbations at 20 cm/sec, with five total diagonal perturbations being unable to be completed. All other diagonal perturbation trials were completed. Trials unable to be completed were excluded from data analysis.

Table 5. Correlation coefficients for during and after diagonal perturbations.

Diagonal Perturbations	10 cm/sec	During	Average	0.86*
			Minimum	0.86*
		After	Average	0.24
			Minimum	0.17
	20 cm/sec	During	Average	0.61
			Minimum	0.79*
		After	Average	0.36
			Minimum	0.42

*Statistically significant, $p < 0.05$.

The relationships between average and minimum VTC and vibration threshold during (Figure 18A) and after (Figure 18B) diagonal perturbations at 10 cm/sec are shown below.

Significant relationships were found during the perturbation for both average VTC and minimum VTC with vibration threshold ($r = 0.86$ and 0.86 for both, $p < 0.05$). No significant relationships were found after diagonal perturbations at 10 cm/sec.

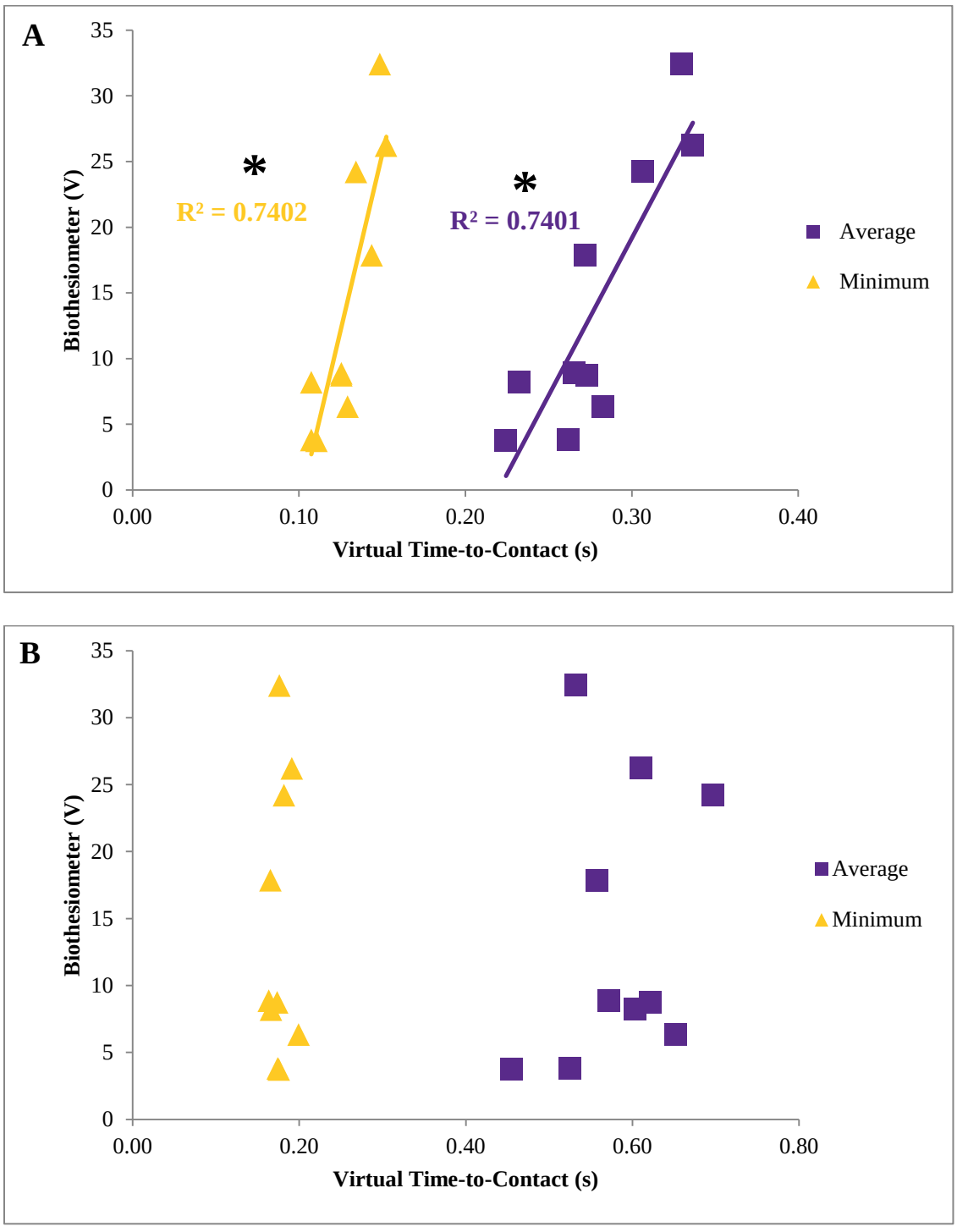

Figure 18. **A.** Average and minimum VTC versus vibratory threshold during diagonal perturbations at 10 cm/sec. **B**. Average and minimum virtual VTC versus vibratory threshold after diagonal perturbations at 10 cm/sec. * Statistically significant, $p < 0.05$.

The relationships between average and minimum VTC and vibration threshold during (Figure 19A) and after (Figure 19B) diagonal perturbations at 20 cm/sec are shown below. A significant relationship was found during the perturbation for minimum VTC with vibration threshold ($r = 0.79$, $p < 0.05$). No significant relationships were found after diagonal perturbations at 20 cm/sec.

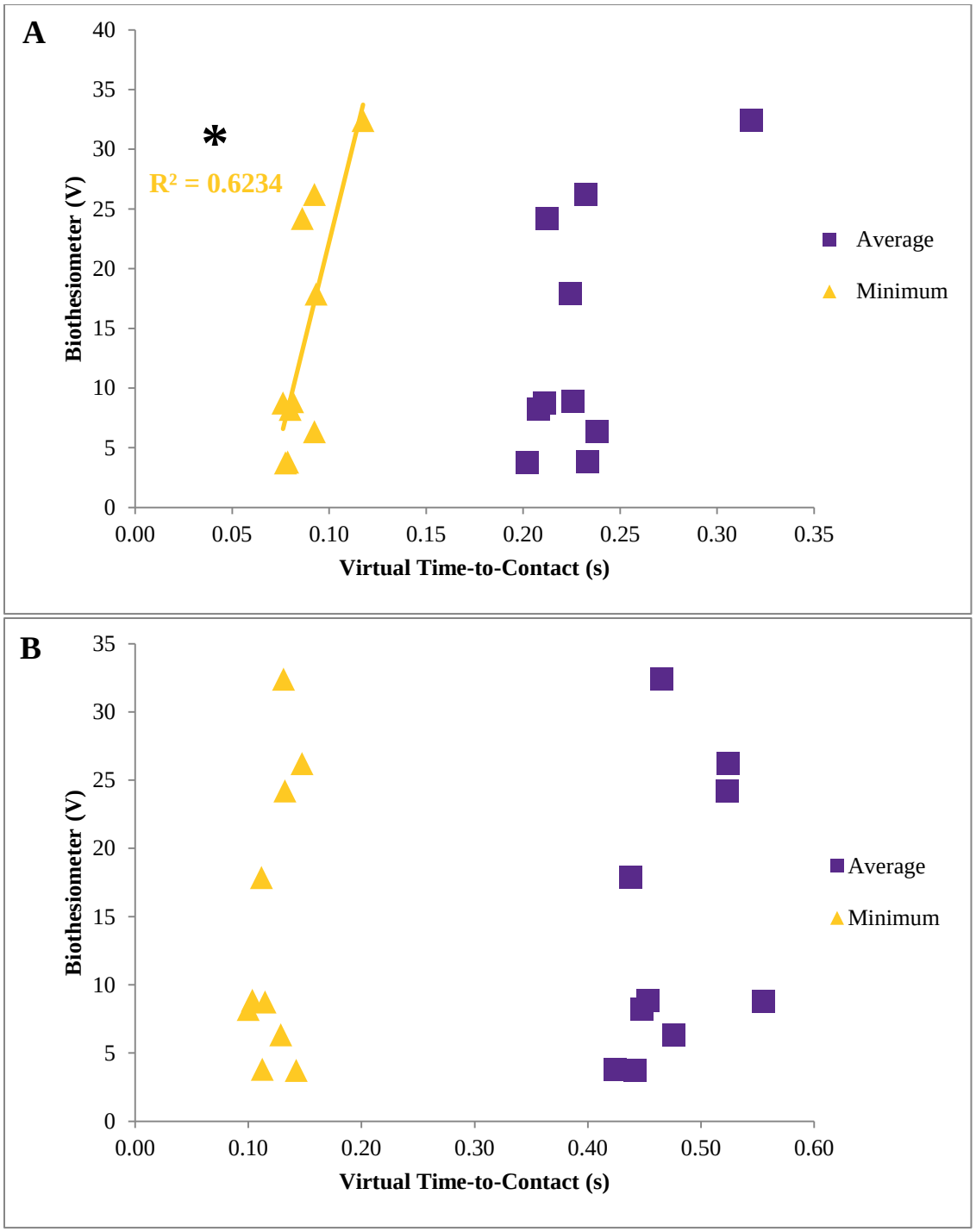

Figure 19. **A.** Average and minimum VTC versus vibratory threshold during diagonal perturbations at 20 cm/sec. **B**. Average and minimum virtual VTC versus vibratory threshold after diagonal perturbations at 20 cm/sec. * Statistically significant, $p < 0.05$.

The average and minimum VTC with standard deviation error bars during and after diagonal perturbations at 10 cm/sec are shown below for the reader's information (Figure 20).

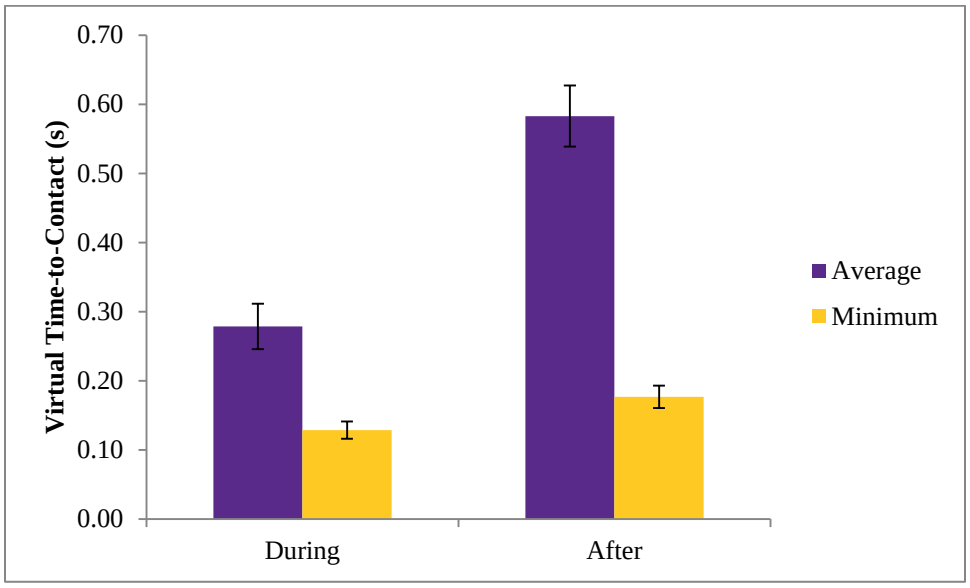

Figure 20. Average and minimum VTC during and after diagonal perturbations at 10 cm/sec.

The average and minimum VTC with standard deviation error bars during and after diagonal perturbations at 20 cm/sec are shown below for the reader's information (Figure 21).

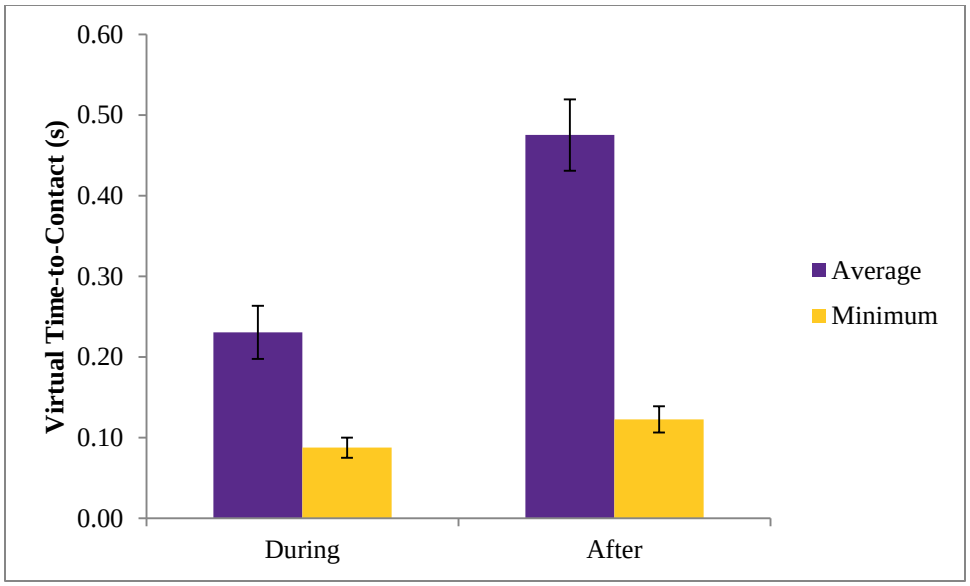

Figure 21. Average and minimum VTC during and after diagonal perturbations at 20 cm/sec. * indicates significant relationship with severity of neuropathy ($p < 0.05$).

A root mean square was calculated for the significant relationships between VTC and diagonal perturbations across both perturbation speeds. The root mean square was r = 0.84. On average, VTC can predict ~71% of the variance in neuropathy severity across the significant relationships during and after diagonal perturbations.

Summary

This study used 10 participants, 5 with diabetes and no diabetic neuropathy and 5 with diabetic neuropathy. Diabetic neuropathy severity was assessed using vibration threshold testing on five plantar surface testing sites on both left and right feet. For each participant, the foot with the higher vibratory threshold was determined to be their neuropathy severity, and was used for all correlations.

The first purpose of this study was to compare how VTC and sway excursion were related to neuropathy severity during and after AP and ML perturbations. We hypothesized that VTC would provide a more sensitive measure of postural stability for people with diabetes and diabetic neuropathy during and after AP and ML perturbations. For AP perturbations, two significant correlations were found. Neuropathy severity was correlated with average VTC during AP perturbations at both 10 cm/sec and 20 cm/sec. AP sway excursion was not correlated with neuropathy severity during or after AP perturbations at either speed.

For ML perturbations, three significant correlations were found. Neuropathy severity was correlated with average and minimum VTC during ML perturbations at 10 cm/sec and was also correlated with minimum VTC during ML perturbations at 20 cm/sec. ML sway excursion was correlated with neuropathy severity during ML perturbations at 20 cm/sec. We think that this provides strong support for the first hypothesis.

The second purpose of this study was to identify the relationship between VTC and neuropathy severity during and after diagonal perturbations. We hypothesized that as neuropathy severity increased, postural stability in response to diagonal perturbations would decrease. For diagonal perturbations, three significant correlations were found. Neuropathy severity was correlated with average and minimum VTC during diagonal perturbations at 10 cm/sec and with minimum VTC during diagonal perturbations at 20 cm/sec. This hypothesis was not supported, based on the current understanding that lower VTC is indicative of lower levels of postural stability.

Chapter 5 – Discussion

Introduction

This study was conducted to evaluate the ability of postural control measures to assess disease severity in people with diabetes and diabetic neuropathy in response to postural perturbations. We compared virtual time-to-contact and center of pressure sway excursion to disease severity. Our research methods were designed to assess differences in postural responses to perturbations in people with a range of diabetic neuropathy, ranging from people with diabetes and no neuropathy to people with moderate to severe diabetic neuropathy. These people were perturbed at two speeds, 10 cm/sec and 20 cm/sec, to elicit postural responses to perturbations in the anteroposterior and mediolateral planes and at 45^{o} diagonal angles. This chapter will discuss the results and related literature and hypotheses.

Anteroposterior & Mediolateral Perturbations

The first purpose of this study was to compare the relationships of both sway excursion and time-to-contact (VTC) with neuropathy severity during and after anteroposterior (AP) and mediolateral (ML) perturbations. We hypothesized that VTC would provide a more sensitive and robust measure of postural stability during and after AP and ML perturbations. We expected that VTC would provide stronger correlations with AP and ML perturbations than sway excursion. We also expected an inverse relationship between VTC and neuropathy severity.

Hasson et al investigated minimum VTC in regards to a threshold for stepping in response to upper body AP perturbations in young and old participants, minimum VTC decreased as the postural challenge increased[62]. The authors found that young participants had to

take a step when minimum VTC was at or below 196 ms, while old participants had to take a step when minimum VTC was at or below 237 ms in response to being perturbed. Thus older adults had to make critical postural adjustments to maintain balance when they had a longer virtual time-to-contact with their support border. This study used a pendulum which perturbed the upper body. Our current study shows that diabetics were able to respond to support-surface AP perturbations without stepping with a minimum VTC of 103 ms, both during and after AP perturbations at 20 cm/sec. Our minimum VTC values are well below Hasson's thresholds for having to take a step. These differences in minimum VTC can be explained either through the height of the perturbation (support surface vs upper body) or through the different method of VTC calculation. The difference in the location or height of the applied perturbing force may elicit different neural responses in terms of which muscles and synergies are activated and the initiation, order and rate of these activations. For example, we conjecture that the time between the upper body perturbation in Hasson et al and the initial sensory response was longer than the corresponding time with our floor perturbation.[62] We used center of pressure (COP), whereas Hasson et al used center of gravity (COG) to calculate VTC. People maintain balance by keeping the COG within the boundary of stability. The COG position is regulated via the position of the center of pressure (COP) and magnitude and direction of the ground reaction force. The ground reaction force emanates from the COP and controls the direction, velocity, and acceleration of the COG. As Winter showed, the COP translates a longer distance and at a higher velocity than the COG; it moves closer to the support border than the COG during postural control activities[29]. We would therefore expect that VTC using COP would be lower than VTC using COG in the same perturbation. These two measures of postural control are

similar but not identical measures. Therefore, it is to be expected to have different minimum VTC values between COP and COG VTC calculations.

Boucher et al found that during quiet standing, people with diabetes and diabetic neuropathy had greater AP (20 mm for diabetic neuropathy group vs 15 mm for healthy control group) and ML (14 mm for diabetic neuropathy group vs 10 mm for healthy control group) sway excursion during quiet standing than healthy controls[7]. They also found that when they grouped participants into healthy, mild neuropathy, and moderate-severe neuropathy groups, as severity of neuropathy increased, AP and ML sway excursion increased during quiet standing across eyes-open and eyes-closed conditions. Control subjects had 12.4 mm of AP sway and 13.5 mm of ML sway. Diabetics with mild neuropathy had 15.5 mm of AP sway and 17.0 mm of ML sway. Diabetics with moderate-severe neuropathy had 21.0 mm of AP sway and 20.1 mm of ML sway. In the present study, a significant relationship was found only between neuropathy severity and ML sway excursion during ML perturbations (ML sway excursion during ML perturbations at 20 cm/sec) and none were found between AP sway excursion and neuropathy severity. Boucher used a different neuropathy scale and split participants into either mild or moderate-severe groups, as opposed to this study, where neuropathy severity was simply regressed with postural stability for each participant. Our study found AP sway excursion as high as 96.3 mm during AP perturbations at 20 cm/sec and ML sway excursion as high as 114.5 mm during ML perturbations at 20 cm/sec. Boucher investigated people during quiet standing, whereas we investigated dynamic perturbations. In a dynamic situation such as a perturbation, it is to be expected that the COP moves through a larger area to maintain balance as a person responds to new forces.

We have support for our first hypothesis in that we found six statistically significant correlations between neuropathy severity and VTC and only one significant correlation between neuropathy severity and sway excursion ($p < 0.05$). The correlations were as follows: average VTC during AP perturbations at 10 cm/sec and 20 cm/sec, average VTC during ML perturbations at 10 cm/sec, minimum VTC during ML perturbations at 10 cm/sec and 20 cm/sec, and ML sway excursion during ML perturbations at 20 cm/sec (Tables 3 & 4). An average correlation coefficient was calculated using the RMS procedure for the five relationships involving VTC and found to be $r = 0.71$. When VTC can predict the variance in neuropathy severity level during and after AP and ML perturbations, it can predict 50% of the variance in in neuropathy severity. In the one instance where sway excursion was significantly related to neuropathy severity, it could predict ~45% of the variance in neuropathy severity. It is important to note that sway excursion had an inverse relationship with neuropathy severity, which was unexpected, while every relationship between VTC and neuropathy severity was a direct relationship, which was also opposite from what was expected as discussed below.

Diagonal Perturbations

The second purpose of this study was to identify the relationship between neuropathy severity and VTC during diagonal translational perturbations. We hypothesized that as neuropathy severity increased, postural stability in response to diagonal perturbations would decrease, as assessed via lower average VTC. As with AP and ML perturbations, we expected an inverse relationship between VTC and neuropathy severity.

We found three significant relationships ($p < 0.05$) between neuropathy severity and VTC during diagonal perturbations: average and minimum VTC during perturbations at 10 cm/sec and minimum VTC during perturbations at 20 cm/sec (Table 5). An average correlation coefficient

was calculated for these three relationships using the RMS procedure and found to be $r = 0.84$. When VTC can predict the variance in neuropathy severity level during and after diagonal perturbations, it can predict ~70% of the variance in neuropathy severity. All of these relationships were positive, meaning that VTC actually increased as neuropathy severity increased. This direct relationship was consistent with our results for both AP and ML perturbations but was unexpected, as lower VTC has been thought to be indicative of lower stability[12,16,62-64]. Previous thought has been based primarily off of VTC under quiet standing conditions or in response to dynamic movements, and not during a dynamic movement. This second hypothesis was not supported.

This decreased COP excursion is shown in the example stabilograms below (Figures 22A & 22B). Figure 22A is from a participant with diabetes and no neuropathy in response to a backwards perturbation at 20 cm/sec. Figure 21B is from a participant with diabetic neuropathy in response to a backwards perturbation at 20 cm/sec. Note the smaller range of COP movement in Figure 22B, which we conjecture is due to the participant with neuropathy having greater co-contraction and whole-body rigidity in response to the perturbation. Increased co-contraction and whole-body rigidity are discussed in the next section below. The trajectories in the figures below are actual trajectories of the center of pressure, not virtual trajectories used to calculate virtual time-to-contact.

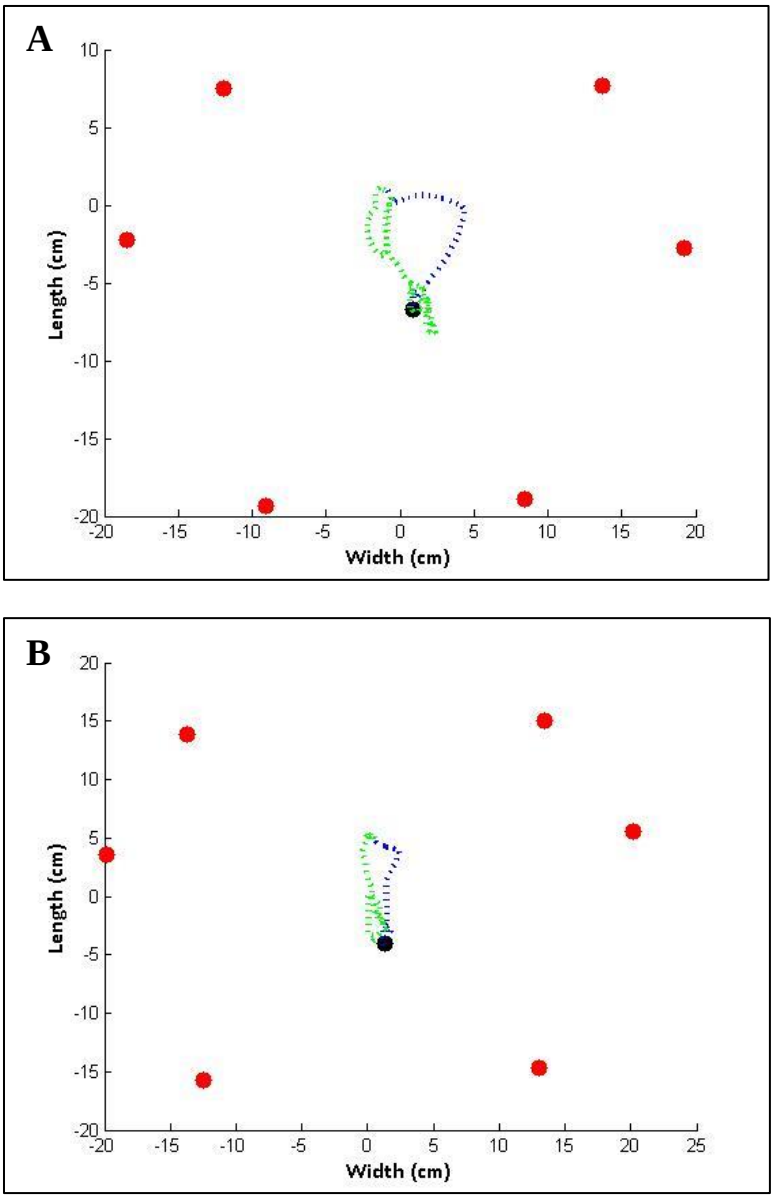

Figure 22. **A**) Example center of pressure stabilogram for a participant with diabetes and no neuropathy during and after a backwards perturbation at 20 cm/sec. **B**) Example center of pressure stabilogram for a participant with diabetic neuropathy during and after a backwards perturbation at 20 cm/sec. The black dot is the starting COP position. The dotted blue line is the COP trajectory during the perturbation. The dotted green line is the COP trajectory after in the perturbation. The red dots are the locations of the reflective markers on the feet used to create the boundary of stability and were at the left and right 1st toes, 5th metatarsal heads, and posterior heels.

This also supports our finding that ML COP sway excursion decreased as disease severity increased during ML perturbations at 20 cm/sec. It is important to note that sway excursion and VTC are independent postural assessments. Sway excursion merely measures the range of sway of the position of COP. VTC takes into account position as well as velocity and acceleration of the COP. Our research found nine relationships between VTC and neuropathy severity and only one relationship between sway excursion and neuropathy severity. This all points to the importance of both the COP velocity and acceleration in assessing postural stability.

Similarities in Responses to Perturbations between People with Diabetic Neuropathy and Parkinson's Disease

Parkinson's disease is a neurological condition as is diabetic neuropathy. People with these conditions have similar postural responses to perturbations. Due to the lack of literature on postural responses to perturbations in people with diabetes and diabetic neuropathy, we suggest that our results can also be explained by similar studies that investigated perturbed standing in people with Parkinson's disease.

Horak et al investigated postural responses to AP perturbations in people with induced ischemia to simulate somatosensory loss in the lower limbs and EMG was used to find that there was greater muscle activation and co-activation in the upper legs and trunk in response to perturbations in the ischemic condition[21]. These are the muscle groups associated with a hip strategy of postural stability. This study used differing velocities of perturbations, but even at lower perturbation displacements (1.2 cm and 6 cm), participants with somatosensory impairments used the muscles of the thighs and trunk to maintain balance. Healthy participants

in this study didn't use the muscles associated with a hip strategy with support surface displacements of 12 cm or less. Our study used perturbations with support surface displacements of 5 cm and 10 cm. Dimitrova et al investigated muscle response activity in people with Parkinson's disease in response to AP, ML, and diagonal perturbations[65]. They found that people with Parkinson's disease had shorter muscle onset latencies of 15-30 ms of antagonist muscles than healthy controls in response to perturbations. This decreased muscle onset latency period results in greater co-contraction. This increased co-contraction leads to increased axial rigidity, or a "freezing" response of the body. This increased rigidity decreases the body's degrees of freedom to be able to effectively respond to a perturbation in order to maintain balance without moving the feet. The reduction in degrees of freedom is a way to maintain postural stability, as having greater degrees of freedom of movement (movement about more joints of the body) is associated with reduced postural stability. This is in perfect alignment with previous literature [21,65]. This provides evidence for similarity in postural responses between people with diabetic neuropathy and Parkinson's disease for perturbed standing.

Inglis et al investigated the ability of people with diabetic neuropathy to scale their postural responses to backward support-surface perturbations[46]. That study found that people with diabetic neuropathy had a higher rate of torque change than healthy controls in response to backwards perturbations at 10 cm/sec, but had lower rates of torque change than healthy controls in response to backwards perturbations at 35 cm/sec. Inglis et al also used EMG in their study[46]. Using EMG, they found delays in the onset of muscle responses in response to perturbations in people with diabetic neuropathy in the gastrocnemius (17 ms compared to controls), hamstrings (20 ms compared to controls), and paraspinalis (29 ms compared to controls). These delays in onset of muscle responses were all found to be statistically significant. EMG was only applied to

these three muscle groups, and not any antagonist muscle groups. This eliminates finding any kind of elevated co-contraction in agonist and antagonist muscle groups, as found above by Horak et al and Dimitrova et al[21,65]. These studies provide evidence that people with diabetic neuropathy have difficulty appropriately scaling postural responses to perturbations. They also have delayed muscular responses and increased co-contraction of agonist and antagonist muscle groups in the lower body. We speculate that this increased co-contraction in the legs and trunk is a response mechanism to unstable situations for people with decreased somatosensory response in the lower limbs. This co-contraction stiffens their lower extremities but also prevents them from effectively changing their COP position, thus limiting their ability to redirect their COG. This decreased COP displacement has a slower velocity, and therefore causes higher average and minimum VTC in participants with greater neuropathy severity. By definition, they have less proprioception and somatosensory feedback, which results in inappropriate scaling of postural responses and they compensate by adopting a safe balance strategy with high levels of co-contraction in the major muscle groups around the hips and trunk.

Horak et al investigated direction-specific stability issues in people with Parkinson's disease[66]. In response to 1 second perturbations at 2 cm/sec that went forwards, backwards, left, right, and at 45^{o} diagonals, people with Parkinson's disease had significantly less peak COP displacement in in all directions. They also had increased peak COG displacement. The decreased peak COP displacement combined with the increased COG displacement resulted in a smaller stability margin and thus decreased postural stability in response to perturbations for people with Parkinson's disease. This was attributed primarily to increased axial rigidity in response to perturbations, as described above by Dimitrova et al[65]. People with Parkinson's disease had ~5.8 cm of peak COP displacement in response to AP perturbations and ~8.1 cm of

peak COP displacement in response to ML perturbations. In the present study with people with diabetes and diabetic neuropathy, we saw average peak COP displacements of ~9.0 cm and ~12.0 cm in response to AP perturbations at 10 cm/sec and 20 cm/sec, respectively, and of ~9.5 cm and ~15.0 cm inn response to ML perturbations at 10 cm/sec and 20 cm/sec, respectively. Our perturbations were at higher velocities, so the increased peak COP displacement is to be expected. Also, we saw higher peak COP displacements in response to ML perturbations than AP perturbations. This is the same pattern as Horak et al found in people with Parkinson's disease[66]. The inability of people with Parkinson's disease to effectively alter their COP position in response to perturbations creates greater instability, as they are less able to appropriately redirect their COG when responding to perturbations. This offers a plausible explanation for our results, in that a population with a neurological disorder showed a decreased peak movement of the COP which would result in lower COP velocity. This lower COP velocity would result in lower COP acceleration and higher average VTC.

Research into perturbed standing responses in people with Parkinson's disease and induced somatosensory loss of the lower body has helped to provide a plausible explanation of the results shown in the current study. People with diabetic neuropathy respond to perturbed standing by employing a "freezing" strategy of postural co-contraction, most likely activating the agonist and antagonist muscle groups of the lower body and trunk causing increased whole-body rigidity. This decreases their degrees of freedom, allowing them to maintain postural stability. Reductions in peak COP displacement show that they are less able to control the displacement of their COP as well as healthy controls, and thus are less able to modulate displacement of their COM.

Limitations

The present study had several limitations. The first limitation was the relatively small sample size of only ten participants. Even with a small sample size, there was enough statistical power to find nine statistically significant relationships between neuropathy severity and postural stability measures. Another limitation was the inability to use the nerve conduction velocity test to test for neuropathy. It is currently the gold standard when testing for neuropathy, but must be completed by a neurologist. This leads to another limitation, which is the assessment and classification of neuropathy. There are multi-faceted neuropathy scales, like the Valk Scale, but the present study used only basic clinical sensory threshold tests to quantify neuropathy severity. The authors think that using clinical tests provides for a direct application of the results to clinicians who only have access to sensory threshold tests. The results of this study are more directly applicable to them. Another limitation lies within the perturbations themselves. Because the participants were secured to a safety harness and were given a general idea of what to expect and a general idea of when to expect a perturbation, the results of this study may not precisely simulate real-world applications. In the real world, people may not know when a support-surface perturbation is going to happen. It may happen unexpectedly. This is especially the case during our protocol when participants could not maintain their balance without stepping during a perturbation and were told to expect that same perturbation a second or third time. This leads to another limitation, in that we excluded perturbation trials from further analysis where participants had to move their feet to maintain balance. We had to exclude ten trials from AP perturbations at 20 cm/sec, but none of the ML perturbations were excluded. This could skew the relationships between VTC and disease severity in response to AP perturbations at 20 cm/sec.

Two limitations that affect the direct comparison to other studies using the diabetic population are an absence of quiet standing data and a lack of a healthy control population. For this study, we used people with diabetes and no neuropathy as control subjects, because we were investigating the effect of diabetic neuropathy on postural control, not diabetes. The vast majority of research investigating postural control in this population uses quiet standing instead of perturbed standing. We assumed that healthy controls would have better postural control (ie: decreased AP and ML sway and higher average and minimum VTC) during and in response to perturbations. However, it was also expected that postural stability would be inversely related to diabetic neuropathy severity. In all of the significant relationships that we found, both average and minimum VTC were directly related to neuropathy severity. Because of this unexpected result, it would have been prudent to be able to investigate how healthy control participants compared to participants with diabetes and diabetic neuropathy using our protocol and analysis techniques.

Another limitation deals with one of the major assumptions of time-to-contact itself. The boundary of support has always been assumed to be defined by the outside of the feet for bilateral standing. However, as the center of pressure approaches the traditionally-defined boundary, there comes a point where either the center of pressure is too close to the boundary for a person to effectively reverse the COP trajectory. Also, as the COP approaches the boundary, there reaches a point where the boundary itself changes. An example of this is if the COP is moving towards the anterior aspect of the boundary, a person will naturally come up on their toes, thus changing the boundary of stability from the area encompassing the feet from heel to toe as the area encompassing the forefoot and toe region, from the metatarsal heads to the toes. The same holds true as the COP approaches the posterior aspect of the boundary without slowing

down or changing direction of the COP trajectory. In this case, a person might have to rock back on their heels, thus shrinking the boundary area to the area encompassed just by the heels. This traditionally-defined boundary also becomes problematic for VTC calculations that use the center of gravity instead of the COP. As the COG approaches the boundary, there comes a point before it contacts the boundary where the COP cannot effectively redirect the COG back towards the center of the area encompassed by boundary of stability. There must be a more practical boundary within the area encompassed by the feet that both the COP and COG cannot cross. Slobounov et al calculated average VTC using both the traditional boundary and a functional boundary that was located within the traditional boundary[63]. That study investigated quiet standing in the elderly and calculated a functional boundary by having the participants oscillate as far forward, back, and to the side as they could. The boundary of the COP during those movements was considered to be the functional boundary. When average VTC was calculated using COP, reductions in average VTC were between ~175 and ~200 ms. Changing the boundary of stability to a more functional boundary would show reductions in VTC values, but would not change the overall conclusion.

Summary

The results from this research showed VTC was related to disease severity of diabetic neuropathy. We found nine significant relationships between disease severity of diabetic neuropathy and virtual time-to-contact ($p < 0.05$). These nine relationships were found during and after anteroposterior, mediolateral, and diagonal perturbations at 10 cm/sec and 20 cm/sec. Our first hypothesis was supported in that we found six relationships between disease severity of diabetic neuropathy and VTC and only one relationship between disease severity of diabetic neuropathy and sway excursion ($p < 0.05$). This shows that VTC can be utilized to assess

neuropathy severity across a range of perturbations. However, VTC was directly related to neuropathy severity, which was contrary to what was expected. Our second hypothesis was not supported, in that as neuropathy severity increased, so did VTC. However, we did find three significant relationships between neuropathy severity and VTC ($p < 0.05$).

We believe that our findings can be best be explained by research done on people with Parkinson's disease that found that people with Parkinson's disease are less able to manipulate their center of gravity via less movement of their center of pressure and employ a "freezing" postural strategy in response to perturbed standing[65,66]. This reduced movement of the center of pressure, and consequent reduction in center of pressure velocity, would explain the direct relationship between neuropathy severity and VTC. This also points to the importance of the velocity and acceleration of the center of pressure in the assessment of postural stability.

The results from this research show virtual time-to-contact can be used to predict disease severity in people with diabetic neuropathy in response to short postural perturbations. VTC is also a more robust measure of postural control than center of pressure excursion in people with diabetic neuropathy, as evidenced by eight significant relationships found between VTC and neuropathy severity compared to the one significant relationship found between sway excursion and neuropathy severity ($p < 0.05$). On average, virtual time-to-contact can explain ~58% of the variation in the neuropathy severity.

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Appendix A-East Carolina University, University and Medical Center Institutional Review Board Letter of Approval

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board Office
4N-70 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** · www.ecu.edu/irb

Notification of Amendment Approval

From: Biomedical IRB
To: Paul DeVita
CC: Stacey Meardon
Date: 2/28/2015
Re: Ame2 UMCIRB 14-000020
UMCIRB 14-000020
Postural Responses to Perturbations in People with Diabetic Peripheral Neuropathy

Your Amendment has been reviewed and approved using expedited review for the period of 2/27/2015 to 11/5/2015. It was the determination of the UMCIRB Chairperson (or designee) that this revision does not impact the overall risk/benefit ratio of the study and is appropriate for the population and procedures proposed.

Please note that any further changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. A continuing or final review must be submitted to the UMCIRB prior to the date of study expiration.The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
Announce Daily Reflector Announcements R2 - Feb 2015.docx(0.01)	Recruitment Documents/Scripts

The Chairperson (or designee) does not have a potential for conflict of interest on this study.
