# THE EFFECT OF COMBINED SERIAL CASTING AND BOTULINUM TOXIN-A INJECTION ON ANKLE EQUINUS IN CHILDREN WITH SPASTIC DIPLEGIA

by

Kelly Stephanie Moore

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Department of _Education (School of Human Kinetics)_

The University of British Columbia
Vancouver, Canada

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# ABSTRACT

This prospective study examined the effects of combined serial casting and botulinum toxin A (Btx) with Btx injection alone in children with spastic diplegia over a 24-week period. Outcome was detemined by the Modified Ashworth Scale, ankle and knee joint ranges of motion, GMFM, gait analysis, and calculation of soleus and gastrocnemius muscle lengths. A decrease in ankle plantarflexor tone and increase in passive ankle dorsiflexion were observed 8 weeks post-injection in both groups and persisted in the combined group until 18 weeks. Improvements in gait were observed only in the combined group at 8 weeks post injection. Examination of these data on a case-by-case basis revealed that 2 of the 5 patients in the Btx only group had improvements in gait that were still evident at 18 weeks post-injection. Improvements in gait persisted in the combined treatment group to 24 weeks. It was concluded that combining Btx with serial casting does lead to more persistent improvements than Btx alone and that combining the two treatments has the potential to be effective in more patients than Btx alone.

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# CHAPTER 1: INTRODUCTION

## 1.1 CEREBRAL PALSY

Cerebral palsy is a non-progressive motor disorder secondary to finite central nervous system insult, usually occurring before, during, or shortly after birth, characterised by an inability to fully control motor function, particularly muscle control and coordination. No cure exists, nor is one imminent.

Cerebral palsy can be grouped into 4 main categories (Mutch et al., 1992): spastic, athetoid, ataxic, and mixed. Spastic cerebral palsy accounts for approximately 70% of all cases. In spastic diplegia, the legs maintain greater spasticity and weakness than the arms. Muscle hypertonicity, abnormal timing and recruitment of muscles, weakness, reduced equilibrium, and reduced joint motion or joint deformity due to dynamic and static muscle contractures contribute to their impaired mobility and increased energy consumption (Gage, 1991; Rose, Ralston, and Gamble, 1994; Damiano and Abel, 1998). Depending on the site and extent of the brain injury, these peripheral manefestations occur either singularly or in combination (Koman et al, 1994).

In the lower extremity, imbalance results most frequently in varying degrees of hip flexion and adduction deformity, knee flexion, and ankle plantarflexion (equinus). Decreased ankle joint range of motion and ankle equinus as a consequence of ankle plantarflexor spasticity are the most recorded and noticeable impairments (Cosgrove et al., 1994; Abel and Damiano, 1999; Koman et al., 2000). Over time, these sustained imbalances of spasticity-induced joint positioning result in further shortening of the spastic/agonist muscle and an increase in the resting length of the relatively hypotonic or antagonist muscle groups with subsequent further weakening (Koman 1994). These changes in turn result in further imbalances that lead to dynamic joint contractures and if full range of motion of the joint is not maintained by active motor power or passive assistance, fixed contractures and/or bony deformities will result.

This results in inappropriate internal muscle moments that interfere with stability in the stance phase of gait. In first rocker, the heel contacts the floor and acts as the fulcrum as the foot is lowered to the ground under eccentric control of the ankle dorsiflexors. At heelcontact, an internal plantarflexor moment due to spasticity causes the foot to land flat or in an equinus position instead of with the heel. First rocker, then, ceases to exist as there is no heel contact. During second rocker, the tibia progresses over the base of support (foot) causing the ankle to dorsiflex under eccentric control of the triceps surae muscle group. When the ankle plantarflexors are spastic, this movement is restrained as the vertical ground reaction force passes anterior to the knee, resulting in an excessive extension moment of the knee. One of two adaptations will take place because of the biarticular role of the tricep surae (due to the gastrocnemius muscle). Either the knee will hyperextend or there will be premature heelrise and the child will bear the weight on his or her toes instead (i.e. early progression to third rocker, where the fulcrum is the MTP joints). In third rocker, when the fulcrum is the metatarsal phalangeal joints, the plantarflexors contract concentrically to propel the body forward. When these muscles are spastic, the internal muscle moment is too large causing the knee to remain extended which results in the body being propelled more upwards than required. Alternatively, if there is an inadequate muscle moment produced by the triceps surae muscle group in third rocker, there will be a persistent crouch and the hip flexors will pull the limb into swing instead of the ankle plantarflexors. The net result of this action is that more energy is consumed.

The goals of treatment in children with cerebral palsy are to maximize function and minimize the secondary effects of the affliciton, such as joint contracure and other musculoskeletal malformations, by promoting longitudinal muscle growth (Reimers, 1990; Cosgrove, Corry, and Graham, 1994), and to delay or prevent orthopedic surgical intervention (Koman et al, 1993; Russman Tilton, and Gormely, 1997; Koman et al., 2000). The ability to walk is a major concern for parents. Improving or maintaining this ability while simultaneously inhibiting the influence of abnormal muscle tone and reflex patterns are often considered to be the primary focus of most therapeutic interventions addressing the motor deficits in these children.

Muscle-tendon lengthening is often performed on children with contractures of the ankle plantarflexors to facilitate walking and normal growth and development (Bleck, 1987). Because growth and maturation factor into the outcome, less invasive methods are attempted in order to delay surgery (Rattey et al., 1993). Two such treatments that are commonly used to delay surgery are serial casting and botulinum toxin injeciton (Btx).

## 1.2 SERIAL CASTING

Serial casting is a conservative treatment for ankle equinus resulting from contracture. The ankle joint is immobilized with the triceps surae subjected to stretch. The primary benefit of serial casting is to increase the length of the spastic triceps surae muscle group. Secondarily, serial casting acts to return ankle motion to a more normal range (i.e. decrease ankle equius). The gait of children receiving serial casts is temporarily improved after removal (Corry, et al., 1998; Flett et al., 1999). Serial casting is reported to prevent excessive ankle plantarflexion and normalize lower-extremity muscle timing (Carlson, 1984), normalize movements of the trunk, pelvis, hip, knee, and ankle (Cusick and Sussman 1982; Duncan and Mott 1983; Hylton 1990), improve foot floor contact (Watt et al, 1986), and increase stride length (Bertoti 1986; Hinderer et al., 1988). Serial casting postpones the likelihood of fixed contractures occurring in the triceps surae muscle group by lengthening the muscles and allowing a more normal range of motion at the ankle joint.

The mechanical stretch induces muscle lengthening through the serial addition of sarcomeres in the muscle fibres (Williams and Goldspink, 1971). When a musculo-tendinous unit experiences permanent elongation of the series elastic component as a result of being maintained at a length greater than its resting length, it can be expected that both the dynamic and static sensitivities will be altered at a given joint position (Otis, 1985). There will be a decrease in static sensitivity because it will require less external effort to hold the ankle in a given position and there will be a decrease in dynamic sensitivity as the joint functions in a relatively more dorsiflexed position.

In feline studies, muscle lengthening persists for 4 weeks after cast removal after which time the number of sarcomeres in series gradually returns to pre-casting levels (Tabary 1972a; Tabary et al., 1972b; Goldspink et al., 1974). In studies examining the longterm effects of serial casting on children with cerebral palsy, improvement in ankle dorsiflexion during gait lasts up to 12 weeks after cast removal: ankle motion returns to pre-casting range by 12 weeks (Corry et al, 1998).

## 1.3 BOTULINUM TOXIN

Btx reduces the effects of spasticity by decreasing the total force produced by the injected muscle (Forssberg and Tedroff, 1997). The H-relex is not affected (Koman et al., 2000). When injected intramuscularly in therapeutic doses, it produces a partial chemical denervation of the muscle resulting in localized muscle paralysis. Some degree of muscle tension is maintained as not all muscle fibres are affected. It is also reported to decrease coactivation (Bentavoglio, 1999).

In the absence of fixed deformity or rigid joint contracture, Btx can be used to restore across-joint muscle balance by diminishing the effects of spasticity in agonist muscle, thereby facilitating and improving function of the previously weakened and lengthened antagonist muscles. Potential secondary gains are prevention of joint contracture or fixed deformity and alteration of the natural history of the specific motor deficit (Bentavoglio and Albanese, 1999). Btx cannot correct underlying etiological factors involved in spasticity or cerebral palsy nor can it directly imporve function or performance. It can delay surgery until the effects of growth and maturation have a diminished effect on the outcome (Cosgrove et al., 1994; Boyd et al., 2000).

Studies examining the effects of Btx injections in children with cerebral palsy have been emerging in the literature. Studies reporting results from Btx injections into the ankle plantarflexors are summarized in Table 1. Overall, the studies report a reduction in muscle tone and spasticity as measured by the Modified Ashworth Scale in treated muscles and improvements in motion at the affected joint(s) (Koman et al., 1993; Calderon-Gonzalez, 1994; Cosgrove et al., 1994; Corry et al., 1998; Wong, 1998; Flett et

al., 1999, Koman et al., 2000). Ambulatory status and gait mechanics have also improved in many children injected with Btx (Koman et al., 1993, 1994; Cosgrove et al., 1994; Corry et al., 1998; Wong et al., 1998; Flett et al., 1999; Sutherland et al., 1999; Koman et al., 2000). Specifically, ankle position and range of motion during both the stance and swing phases of the walking stride are improved after the ankle plantarflexors are treated with Btx (Corry et al., 1998; Sutherand et al., 1999). These changes are still evident 12 weeks post injection (Corry et al., 1998). Only two studies to date have directly compared the effects of serial casting with Btx (Corry et al., 1998; Flett et al., 1999). Both studies have concluded that Btx and serial casting have similar effects, but that Btx has more persistent effects. These two studies report a decrease in spasticity as measured by the Modified Ashworth Scale and improvements in gait as measured by a physicians rating scale. Improvements in ankle kinematics measured by 3-D gait analysis were reported by Corry et al. (1998). In addition, Flett et al. (1999) report improvements in motor function as measured by the GMFM. Corry et al. (1998) conclude that Btx is at least as effective as casting and has more persistent effects in the conservative management of ankle equinus. There are also fewer side effects reported with the Btx group.

It can be argued that because Btx and casting have different modes of action (Btx decreasing the force-generating capacity of the muscle and casting lengthening the musculo-tendinous unit), the two combined should have a more persistent effect than either alone.

## 1.4 PURPOSE

The purpose of this study was to investigate how Btx alone and a combination of serial casting and Btx impact ankle plantarflexor spasticity, motor functioning, ankle motion, and gait of children with cerebral palsy.

## 1.5 HYPOTHESES

It was hypothesized that improvements in the selected clinical measures and gait parameters of both groups would be evident post-treatment and that the group receiving

the combined treatment of Btx and serial casting would have more persistent effects than the group receiving Btx alone. The specific hypotheses are outlined below.

A. Both groups will respond to treatment with the following improvements:
   i. increased passive dorsiflexion
   ii. decreased ankle tone as measured by the Modified Ashworth Scale
   iii. increased GMFM score
   iv. increased ankle dorsiflexion during gait
   v. time to max dorsiflexion later in stance phase
   vi. no change in knee angle during gait
   vii. decreased vertical GRF
   viii. decreased ankle plantarflexor moment midstance
   ix. decreased maximum ankle plantarflexor moment
   x. decreased ankle power absorption
   xi. decreased ankle power generation
B. the improvements will persist in the combined treatment group longer than the Btx only group

## 1.6   THESIS OVERVIEW

In this thesis, the entire research project is reviewed and discussed. Chapter 2 contains a manuscript that will be sent to the Journal of Pediatric Orthopaedics for publication. It primarily discusses the main portion of this research project concerned with how a combination of Btx and casting affects the gait and various clinical measures in children with spastic diplegia. Chapter 3 evaluates the research project and makes suggestions for future research into this area. Appendix A contains a thorough review of the current literature in this area. Appendix B is concerned with the objective measure of spasticity. It contains a portion of this research project that was not included in the manuscript for publication. Appendix C contains the individual subject data pertaining to gait. Appendix D contains the approved informed consent form used for this study.

# CHAPTER 2: MANUSCRIPT

## 2.1 ABSTRACT

This prospective study examined the effects of combined serial casting and botulinum toxin A (Btx) with Btx injection alone in children with spastic diplegia over a 24-week period. Outcome was detemined by the Modified Ashworth Scale, ankle and knee joint ranges of motion, GMFM, gait analysis, and calculation of soleus and gastrocnemius muscle lengths. A decrease in ankle plantarflexor tone and increase in passive ankle dorsiflexion were observed 8 weeks post-injection in both groups and persisted in the combined group until 18 weeks. Improvements in gait were observed only in the combined group at 8 weeks post injection. Examination of these data on a case-by-case basis revealed that 2 of the 5 patients in the Btx only group had improvements in gait that were still evident at 18 weeks post-injection. Improvements in gait persisted in the combined treatment group to 24 weeks. It was concluded that combining Btx with serial casting does lead to more persistent improvements than Btx alone and that combining the two treatments has the potential to be effective in more patients than Btx alone.

## 2.2 INTRODUCTION

Ankle equinus due to spasticity of the ankle plantarflexors is a common deformity in children with cerebral palsy and adversely affects balance and gait. Maintaining the length of the ankle plantarflexors is paramount to maintaining walking ability and facilitating normal growth and development. Surgery is often performed to lengthen the shortened ankle plantarflexors; however, the earlier the age at surgery, the greater the chance of recurrent equinus (Rattey et al., 1993). Alternate, less invasive treatments are therefore used to delay surgery for ankle equinus (Boyd et al., 2000). Two such treatments are serial casting and botulinum toxin-A (Btx) injection.

Conservative treatment for ankle equinus in cerebral palsy is serial casting. The ankle is maintained in a functional position and the ankle plantarflexors are subjected to stretch. The muscles are lengthened through the serial addition of sarcomeres (Williams and Goldspink, 1978). Casting is reported to return ankle motion to a more normal range, but improvements in gait last for less than 12 weeks after cast removal (Corry et al., 1998).

Btx is a relatively new treatment for spasticity in children with cerebral palsy (Koman et al., 1993). By partially denervating the injected muscle(s), the force-generating capabilities are reduced. Spasticity is not reduced as the H-reflex is not affected (Koman et al., 2000). Btx is reported to decrease muscle tone, promote muscle balance across joints, increase range of motion at the affected joint, improve ambulation, and improve motor functioning (Calderon-Gonzalez et al., 1994; Corry et al., 1998; Cosgrove, Corry, and Graham, 1994; Flett et al., 1999; Koman et al., 2000; Sutherland et al., 1999). Similar results were observed in children after surgical lengthening of the gastrocnemius (Rose et al., 1993). The effects of the Btx begin to relapse by 3-6 months post-injection. The persistent effects of the Btx are often attributed to a lengthening of the injected muscle(s) (Corry et al., 1998; Flett et al., 1999).

Both serial casting and Btx affect different aspects of the spastic muscle, yet their outcomes are similar (Corry et al., 1998; Flett et al., 1999). Btx decreases the effects of

the reflex-induced resistance by partially paralysing the muscle. Casting affects the non-reflex properties (plasticity and visco-elasticity) of the musculotendinous unit through lengthening. Previous publications have commented that since the two treatments have similar effects and Btx has more persistent effects coupled with fewer side effects, Btx can be used in place of casting to treat ankle equinus (Corry et al., 1998; Flett et al., 1999). In addition, casts are often applied if minimal improvement is observed after initial Btx injection (Boyd et al., 2000) and night splints are often used to potentiate the effects of the Btx (Cosgrove, Corry, and Graham, 1994). However, the comparison between Btx injections and a combination of Btx and serial casting has not been reported to date.

In this study, we compared the effects of combined serial casting and Btx injection into the ankle plantarflexors with Btx injections alone in the treatment of ankle equinus in children with spastic diplegia. It was hypothesized that improvements in gait and decreases in spasticity would be more persistent in the group receiving both Btx and casting than in the group receiving Btx alone.

## 2.3  METHODS

### 2.3.1  Subjects

All subjects participating in this study met the following criteria: aged between 5-9 years; diagnosed with spastic diplegia; problems with dynamic equinus due to increased spasticity in the triceps surae; independently ambulatory; candidate for treatment with serial casting; no fixed contractures in the lower extremities (passive ankle dorsiflexion to neutral or beyond); no prior orthopaedic surgery in the lower extremities; and no previous injections of botulinum toxin A.

Eight children between the ages of 5-9 years (7.5 ± 1.5 years, mean ± 1SD) at the time of baseline testing were enrolled in this study. The seven male and one female participant were divided into two groups: Botox only (n=5, aged 7.8 ± 1.6 years) and combined Botox with Casting (n=3, aged 6.9 ± 1.4 years). Two subjects in the Btx only group did

not complete the last testing session at 24 weeks post-injection due to illness. They could not be rescheduled at a later date due to the timing of the study.

### 2.3.2   Btx Injections

Prior to the Btx injection, each subject was given an oral sedative (Versed) and closely monitored until the drug had taken effect. The injection area was pretreated with a topical lignocaine-based anaesthetic (EMLA) to decrease discomfort caused by needle. The Btx (BOTOX, Allergan, Irvine, CA) was prepared by dissolving the toxin in preservative-free saline (1cc/100U vial) to give a resulting concentration of 100U/cc. Under appropriate sterile technique, a 27-gauge needle was placed within the proximal muscle belly and Btx was injected in a fan like pattern into the medial and lateral heads of the gastrocnemius muscles. Five units/kg body mass of Botox were injected bilaterally into each calf for a total of 10U/kg per subject. Following the injection, the children were monitored until the effects of the oral sedative had worn off and were discharged with instructions to observe for any signs general weakness or any other symptom that could be a possible side effect.

### 2.3.3   Serial Casting

Two weeks following the Btx injection, the subjects in the combined group began casting treatment. Each foot was casted with a fibreglass walking cast with the ankle positioned in a neutral to dorsiflexed position, subjecting the ankle plantarflexors to stretch. Two weeks after casting, new casts were applied for an additional two weeks, bringing the total time in casts to 4 weeks.

### 2.3.4   Protocol

The study consisted of four testing sessions in addition to treatment over a 6 month period: pre-treatment, 8 weeks post Btx injection, 18 weeks post Btx injection, and 24 weeks post Btx injection. During each session, data were collected on ankle plantarflexor spasticity, knee and ankle joint range of motion, Gross Motor Function Measure (GMFM), and gait. From these evaluations, selected measures were chosen for statistical analysis.

## 2.3.5 Clinical Evaluation

Joint Spasticity: Ankle joint spasticity was manually measured using the Modified Ashworth Scale detailed by Bohannon and Smith (1). Subjects were barefoot and supine for ankle spasticity assessment and were asked to relax the leg and foot completely. Each ankle was moved passively from a position of full plantarflexion to full dorsiflexion. The physiotherapist's supporting hand stabilized the limb by grasping the leg just proximal to the malleoli with the knee in a flexed position. The opposite hand grasped the foot, with the physiotherapist's palm against the distal plantar aspect of the subject's foot. The ankle motion occurred in the sagittal plane. Movement through the full range of ankle motion lasted about 0.5 seconds. The investigator performed 2-3 repetitions of the ankle movement, resting for a minimum of 15 seconds between each, before assigning a score.

Joint Range of Motion: Ankle and knee joint ranges of motion were measured using a hand-held goniometer. For each measurement, the physiotherapist would properly position the arms of the goniometer and then slowly move the joint through its range of motion so as to not elicit any spastic responses. For ankle measurements, the child lay supine as the physiotherapist manipulated the child's legs. Maximal degree of ankle dorsiflexion was measured two ways: with the knee positioned at 90 degrees to tease out the movement resisted by primarily the soleus and with the knee fully extended to estimated movment restricted by the gastrocnemius. Maximal ankle plantarflexion was measured with the knee fully extended. To measure knee extension, the child lay supine with the hip in a neutral position. The physiotherapist lifted the leg at the ankle to fully extend the knee. The child lay in a prone position for knee flexion measurements.

GMFM: The GMFM was used in order to categorize the motor skill level of these subjects and to detect any changes after treatment. The GMFM is a criterion-referenced test that measures "how much" of a function a child can accomplish. The GMFM evaluates 88 items covering five motor domains: (a) lying and rolling; (b) sitting; (c) crawling and kneeling; (d) standing; and (e) walking, running, and jumping. For the purposes of this study, only the last three sections of the GMFM were used: crawling and kneeling, standing, and walking running, and jumping. The subjects in this study had a

high level of functioning and the last three domains were determined to be the most critical in assessing the effects of the treatment.

An experienced physiotherapist demonstrated each task to the subject and then asked the child to replicate the movement. The child was given three chances to replicate the movement. The criteria were then consulted and a score for that task was recorded.

### 2.3.6 Gait

The subjects were suitably dressed in tight shorts to maximize the amount of markers that were placed directly on the skin and to minimize marker movement. Twenty-one retroreflective markers were placed over various landmarks using the Helen Hayes marker set. Anthropometric measures of height, mass, foot length, and widths of the forefoot, ankle, and knee were taken for appropriate anthropometric scaling.

The gait of all subjects was assessed using a three-dimensional, six-camera, 60 Hz Motion Analysis measurement system (Santa Rosa, CA) and two 1000 Hz AMTI (Watertown, MA) force platforms. The motion analysis lab was calibrated prior to each testing session to reduce errors of marker position to within 1.8mm. Joint centres of the knee and ankle were determined as the mid-distance between the lateral and medial aspects of the individual joint lines.

Subjects were instructed to walk at a self-selected pace ($1.1 \pm 0.1$ m/s, average $\pm$ 1SD) along a 4-m walkway. Complete kinematics and kinetics were collected for five left and five right strides. Because some of the markers were not tracked during the entire stride and the feet did not land entirely on the force platform, some of the collected trials did not satisfy criteria for an accurate trial. Due to these circumstances, the first right and left strides collected at each testing session that satisfied the criteria for a successful trial were selected for further analysis.

The kinematics and kinetics were collected using Motion Analysis EVA v. 5.20 and combined in Orthotrac v.4.1.2 where components of the stride (heelstrike and toe-off)

were determined. Heelstrike was taken to be the frame before which a measureable GRF was recorded and toe-off the frame after which the force platform detected a force. The kinematic data were filtered at 6Hz with a $4^{th}$ order Butterworth filter.

The various kinematic and kinetic variables selected for statistical analysis are listed in Table 2.3.6-1.

*Table 2.3.6-1: List of gait kinematics and kinetics selected for statistical analysis*

Ankle angle
   Heel strike
   Toe-off
   Maximum dorsiflexion in stance
   Time to maximum dorsiflexion in stance
Knee angle
   Heel strike
   Toe-off
   Maximum extension in stance
Vertical Ground Reaction Force (% Body Weight)
   $1^{st}$ peak
Ankle Moment
   Plantarflexor moment midstance
   Peak plantarflexor moment
   Time to peak plantarflexor moment
Ankle Power
   Peak power absorption
   Peak power generation

## 2.3.7 Muscle Lengths

The length from origin to inertion of the gastrocnemius and soleus musculotendinous units during each stride were calculated using the equations of Grieve, Pheasant, and Cavanagh (9). Muscle lengths at heelstrike and toe-off and minimum and maximum lengths during stride were calculated for statistical analysis. These variables correspond to those ankle angle variables that were analysed.

*2.3.8   Statistical Analysis*

Data gathered from the Modified Ashworth measure were analysed using a Friedman's ANOVA for non-parametric data. The remaining data were analysed using a 2(group) x 2(foot) x 4(day) repeated measures ANOVA with repeated measures on the day (pre-, 8 weeks post-, 18 weeks post-, and 24 weeks post-treatment) factor.

## 2.4   RESULTS

*2.4.1   Clinical Findings*

In response to treatment, there was a decrease in ankle plantarflexor tone and an increase in ankle dorsiflexion observed in both groups. Motor function was not altered. Table 2.4.1-1 shows the mean values for each of the two groups at each testing session.

**Table 2.4.1-1: Mean values (±1 SD) of clinical measurements in both groups over the 24 week testing period**

|  | Pre-treatment | 8 wks post-treatment | 18 wks post-treatment | 24 wks post-treatment |
|---|---|---|---|---|
| **Ashworth \*** |  |  |  |  |
| Btx | 1.6 (0.7) | 1.0 (0) | 1.6 (0.5) | 2.0 (0.9) |
| Btx + Cast | 1.8 (0.8) | 1.0 (0) | 1.2 (0.4) | 1.8 (1.0) |
| **Dorsiflexion (knee at 0°) \*$^\Delta$** |  |  |  |  |
| Btx | 3.5° (7.8) | 9.0° (5.7) | 1.3° (7.5) | 2.5° (8.2) |
| Btx + Cast | 7.5° (8.8) | 12.5° (9.4) | 6.7° (11.7) | 17.5° (9.9) |
| **Dorsiflexion (knee at 90°) \*$^\Delta$** |  |  |  |  |
| Btx | 9.5° (6.4) | 11.5° (7.5) | 7.5° (8.9) | 11.7° (4.1) |
| Btx + Cast | 11.7° (10.3) | 20.0° (7.7) | 19.2° (5.8) | 18.3° (8.8) |
| **GMFM** |  |  |  |  |
| Btx | 89.0 (5.0) | 89.9 (4.2) | 91.1 (5.1) | 87.2 (1.1) |
| Btx + Cast | 87.4 (8.4) | 85.8 (3.5) | 90.3 (4.0) | 90.7 (6.9) |

\* significant time effect with value at 8 weeks post-injection significantly different that value pre-treatment
$^\Delta$ significant difference between groups

There were significant decreases in ankle plantarflexor tone as measured by the Modified Ashworth Scale at 8 weeks post-injection in both groups. By 18 weeks post-injection,

ankle plantarflexor tone had returned to pre-injection values in the Btx only group and although not significant (p=0.08), tone was still decreased in the combined group.

Passive ankle dorsiflexion, measured with the knee fully extended and flexed at 90°, was significantly increased in both groups at 8 week post-injection, but the increase was greater in the group receiving both Btx and casting than in the group receiving Btx alone. Passive ankle range of motion was not affected, it was moved to a more dorsiflexed range.

There were no differences between groups or over time in gross motor functioning as measured by the GMFM.

**Table 2.4.1-2:** *Mean values (±1 SD) of ankle kinematics of both groups over the 24-week testing period*

| | Pre-treatment | 8 wks post-treatment | 18 wks post-treatment | 24 wks post-treatment |
|---|---|---|---|---|
| **Ankle angle heelstrike** $^\Delta$ | | | | |
| Btx | -2.8° (4.5) | -4.1° (7.6) | -4.2° (3.7) | -4.5° (8.3) |
| Btx + Cast | -0.4° (6.3) | 4.7° (6.2) | -2.3° (10.4) | 2.7° (7.1) |
| **Ankle Angle toe-off** $*^\Delta$ | | | | |
| Btx | -17.3° (11.5) | -17.2° (13.0) | -17.1° (8.2) | -13.9° (9.9) |
| Btx + Cast | -11.5° (5.2) | 4.1° (4.3) | -7.5° (7.4) | -8.6° (6.4) |
| **Max dorsiflexion stance*** | | | | |
| Btx | 12.1° (4.0) | 9.0° (5.0) | 10.2° (4.0) | 9.2° (8.4) |
| Btx + Cast | 10.6° (4.7) | 16.6° (2.4) | 12.9° (6.7) | 13.9° (7.2) |
| **Time to max dorsiflexion (% stride)** * | | | | |
| Btx | 24.0 (16.8) | 23.6 (14.9) | 25.6 (16.6) | 33.6 (18.3) |
| Btx + Cast | 22.8 (11.7) | 43.1 (14.0) | 28.4 (13.2) | 34.0 (17.8) |

\* significant time effect with value at 8 weeks post-injection significantly different that value pre-treatment
$^\Delta$ significant difference between groups

### 2.4.2 Gait

Gait kinematics and kinetics were altered with treatment. The mean values for the groups at each testing session are show in Tables 2.4.2-1 and 2.4.2-2.

Differences in gait kinematics occurred only at the ankle, there were no statistically significant differences found at the knee. At the ankle, statistically significant changes were only evident in the group receiving both Btx and casting at 8 week post-injection. The combined group exhibited greater ankle dorsiflexion through the gait cycle and maximum dorsiflexion occurred later in the stance phase (Figure 2.4.2-1).

**Table 2.4.2-1:** *Mean values (±1 SD) of gait kinetics of both groups over the 24-week testing period*

| | Pre-treatment | 8 wks post-treatment | 18 wks post-treatment | 24 wks post-treatment |
|---|---|---|---|---|
| **Vertical GRF 1$^{st}$ peak (% body weight) *** | | | | |
| Btx | 1.53 (0.33) | 1.50 (0.30) | 1.58 (0.32) | 1.28 (0.21) |
| Btx + Cast | 1.57 (0.11) | 1.38 (0.15) | 1.42 (0.24) | 1.50 (0.27) |
| **Ankle plantarflexor moment midstance $^{\Delta}$** | | | | |
| Btx | 1.07 (0.23) | 1.02 (0.22) | 1.07 (0.35) | 0.94 (0.30) |
| Btx + Cast | 0.78 (0.19) | 0.61 (0.25) | 0.64 (0.25) | 0.80 (0.21) |
| **Peak ankle plantarflexor moment $^{\Delta}$** | | | | |
| Btx | 1.12 (0.16) | 1.05 (0.15) | 1.17 (0.37) | 1.07 (0.23) |
| Btx + Cast | 0.87 (0.19) | 0.74 (0.14) | 0.85 (0.16) | 0.93 (0.09) |
| **Time to peak ankle plantarflexor moment (% stride)** | | | | |
| Btx | 27.5 (15.5) | 25.0 (15.5) | 27.1 (18.7) | 34.8 (16.1) |
| Btx + Cast | 26.6 (18.6) | 48.4 (3.0) | 31.7 (17.9) | 33.0 (18.8) |
| **Peak ankle power absorption *** | | | | |
| Btx | -2.3 (1.4) | -1.8 (0.9) | -2.4 (1.1) | -1.4 (0.6) |
| Btx + Cast | -1.7 (0.6) | -0.8 (0.3) | -1.6 (1.2) | -1.4 (0.7) |
| **Peak ankle power generation** | | | | |
| Btx | 1.63 (0.45) | 1.38 (0.32) | 1.74 (0.79) | 1.17 (0.21) |
| Btx + Cast | 1.32 (0.74) | 1.13 (0.50) | 1.42 (0.86) | 1.41 (0.67) |

\* significant time effect with value at 8 weeks post-injection significantly different that value pre-treatment
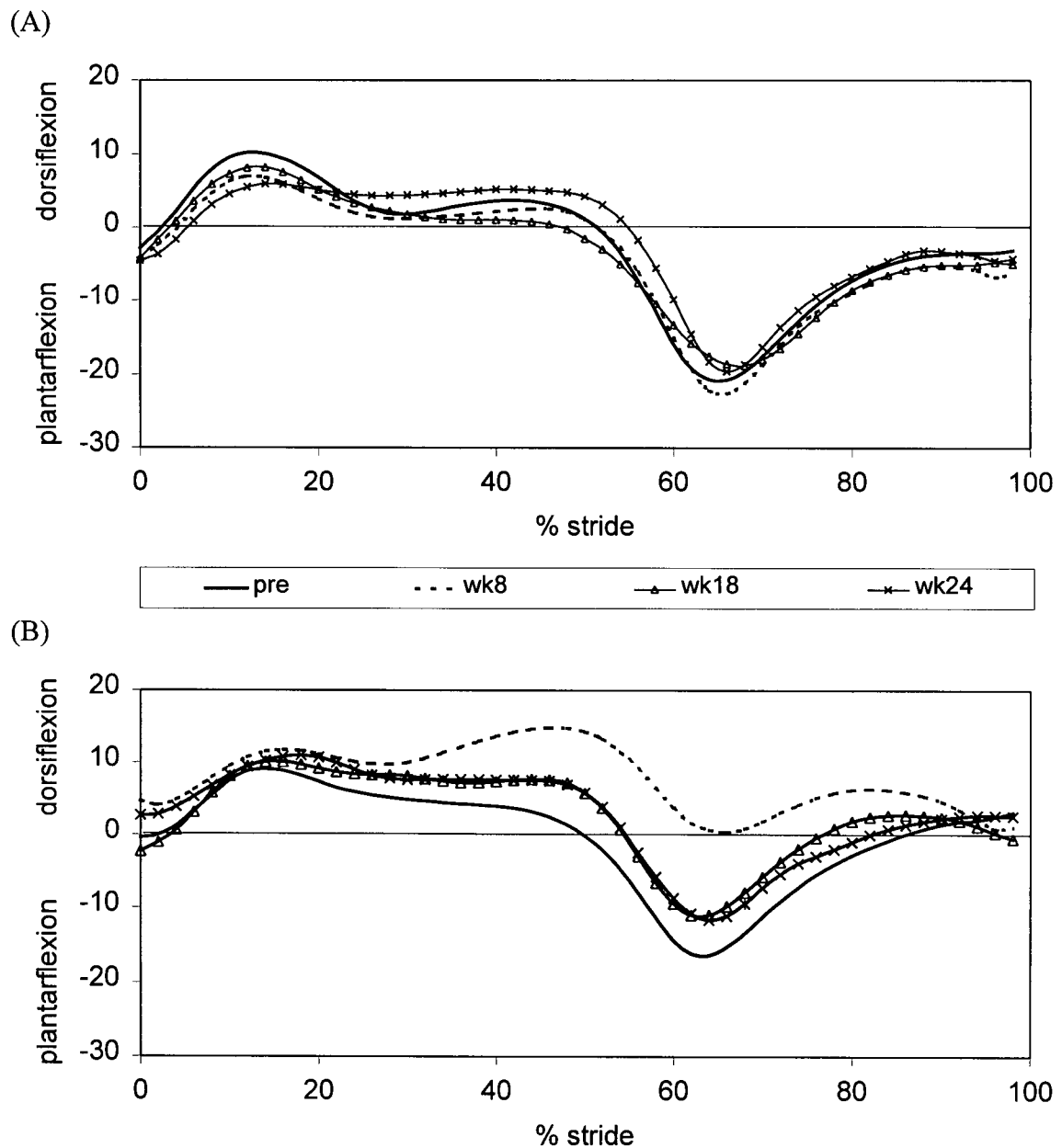$^{\Delta}$ significant difference between groups

(A)



(B)



*Figure 2.4.2-1: (A) Mean ankle angle during one stride of the 5 patients (10 limbs) in the Btx only group before- and at 8-, 18-, and 24-weeks post-injection. (B) Mean ankle angle during one stride of the 3 patients (6 limbs) in the combined treatment group receiving both Btx and serial casting before-, and at 8-, 18-, and 24-weeks post-injection.*

The first peak of the vertical ground reaction force, ankle plantarflexor moment midstance, and peak plantarflexor moment was significantly lower in the combined group than in the group receiving Btx alone. Peak power absorption was decreased at 8 weeks post-injection.

### 2.4.3 Muscle Lengths

Muscle length changes were calculated for the soleus and gastrocnemius muscles during gait (Figures 2.4.3-1 and 2.4.3-2). The changes in muscle length from pre-treatment values are shown in Table 2.4.3-1. The length of the soleus and gastrocnemius musculotendinous units in the combined treatment group were significantly longer at heelstrike and toe-off than in the group receiving Btx alone. These muscles functioned in a longer range in the group receiving both Btx and casting. At 8 weeks post-injection, the length of soleus and gastrocnemius were significantly longer in the combined treatment group at toe-off than in the Btx only group and the minimum and maximum lengths were greater as well. There was no effect on the range of length (maximum length in stance minus minimum length in stance) change in either muscle.

## 2.5 DISCUSSION

This study is the first to examine the effects of combined Btx and serial casting on ankle equinus in children with spastic diplegia. In previous publications, the persistent effects seen after Btx injection have been attributed to an increase in muscle length (4, 8). It was therefore hypothesized that lengthening the ankle plantarflexors with serial casting after Btx injections into that muscle group would lead to more persistent effects than Btx injections alone. The results of this study do support this hypothesis. However, there were only minimal improvements seen in the group receiving Btx alone compared to the group receiving the combined treatment of Btx with serial casting.

A decrease in muscle tone was noted in both groups 8 weeks post-injection but had returned in the Btx only group by 18 weeks post-injection while still evident in the combined group at this time. This decrease in ankle plantarflexor spasticity presumably led to the increase in passive ankle dorsiflexion observed at 8 weeks post-injection in

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both groups and the persistent increase observed in the combined treatment group at 18 and 24 weeks post-injection.

**Table 2.4.3-1:** *Change in soleus and gastrocnemius muscle length from pre-injection values (expressed as a % change in length during the gait cycle)*

| | 8 wks post-treatment | 18 wks post-treatment | 24 wks post-treatment |
|---|---|---|---|
| **SOLEUS** | | | |
| **Heel-strike** $^\Delta$ | | | |
| Btx | -0.27 | -0.27 | -0.35 |
| Btx + Cast | 0.99 | -0.42 | 0.60 |
| **Toe-off** $*^\Delta$ | | | |
| Btx | 0.17 | 0.21 | 0.86 |
| Btx + Cast . | 3.07 | 0.55 | 0.52 |
| **Minimum stance length** $*^\Delta$ | | | |
| Btx | 0.12 | 0.16 | 0.79 |
| Btx + Cast | 2.37 | 0.51 | 0.47 |
| **Maximum stance length** $^\Delta$ | | | |
| Btx | -0.5 | -0.3 | -0.5 |
| Btx + Cast | 1.0 | 0.4 | 0.5 |
| | | | |
| **GASTROCNEMIUS** | | | |
| **Heel-strike** $^\Delta$ | | | |
| Btx | -0.07 | -0.32 | -0.46 |
| Btx + Cast | 0.48 | -0.34 | 0.32 |
| **Toe-off** $*^\Delta$ | | | |
| Btx | 0.17 | 0.16 | 1.01 |
| Btx + Cast | 3.02 | 0.35 | 0.43 |
| **Minimum stance length** $*^\Delta$ | | | |
| Btx | 0.17 | 0.16 | 1.01 |
| Btx + Cast | 2.48 | 0.35 | 0.43 |
| **Maximum stance length** $*^\Delta$ | | | |
| Btx | -0.23 | -0.26 | -0.10 |
| Btx + Cast | 1.8 | 0.72 | 0.37 |

\* significant time effect with value at 8 weeks post-injection significantly different that value pre-treatment
$^\Delta$ significant difference between groups

(A)
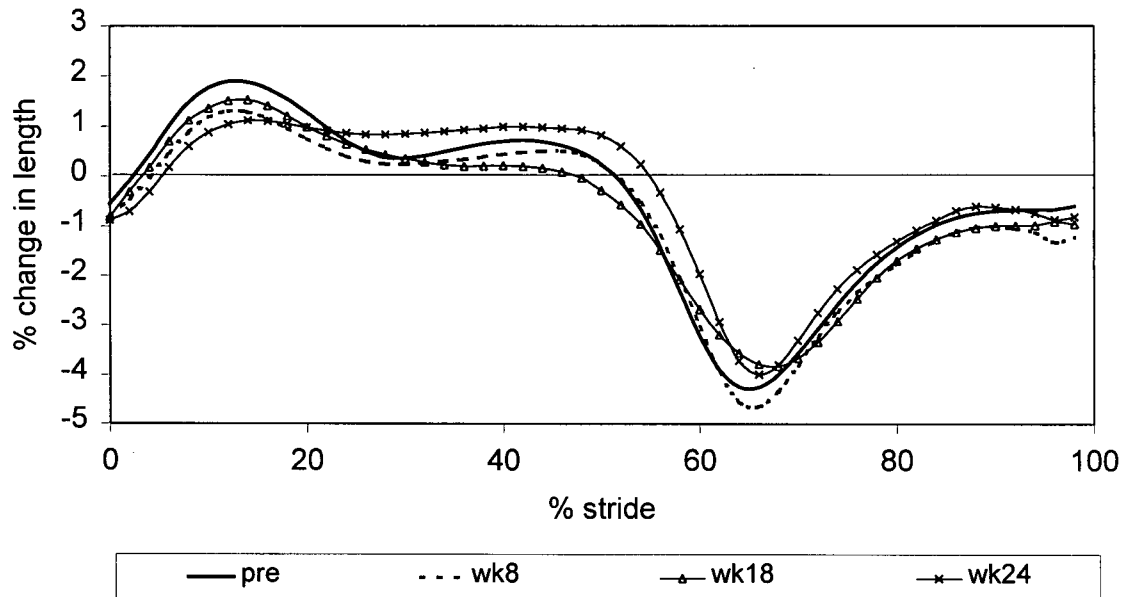


(B)



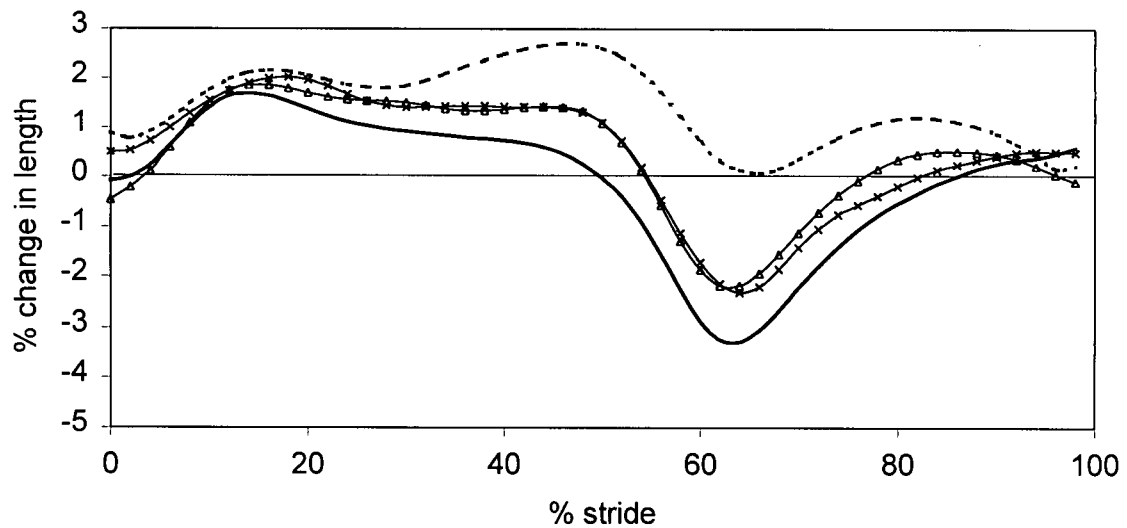*Figure 2.4.3-1:* *(A) Mean calculated soleus length during one stride of the 5 subjects (10 limbs) in the group recieving Btx injections before-, and at 8-, 18-, and 24-weeks post-injection. (B) Mean calculated soleus length during one stride of the 3 subjects (6 limbs) in the combined treatment group before- and at 8-, 18-, and 24-weeks post-injection.*

These passive improvements in ankle function after treatment were only reflected in the gait of the patients receiving both serial casting and Btx. Ankle movement and power absorption were improved during the stance phase of gait at 8 weeks post-injection in the combined group only. This increase in ankle dorsiflexion during stance led to the decreased power absorption observed in this group. The gait of children receiving Btx only was not significantly altered at any of the follow-up sessions.

Because there were no group differences found in the gait of the subjects receiving Btx only, we compared the results on a case-by-case basis. Looking at each subject separately at 8 weeks post-injection reveals that some subjects did not respond to the Btx treatment. In the Btx only group, there was a decrease in ankle plantarflexor tone in only 3 subjects, 5 of the 10 legs injected. Of those 3 subjects, passive ankle dorsiflexion and dynamic ankle dorsiflexion in gait were increased in 2 subjects, for a total of 4 legs. There were corresponding increases in soleus and gastrocnemius muscle length in all four of these legs.

The 4 legs that responded to the Btx injections still showed a decrease in ankle plantarflexor tone at 18 weeks post injection. Again, there were increases in ankle dorsiflexion and gastrocenmius and soleus muscle length during gait. These results cannot be compared at 24 weeks post-injection as these two subjects did not complete the last testing session. Unfortunately, there is only data on muscle tone and passive range of ankle motion at 24 weeks post-injection for one of these subjects. The decrease in ankle plantarflexor tone and increase in passive ankle dorsiflexion was still evident at this time. This subject was unable to complete the gait analysis and the other responding subject did not attend the last session.

From these data, we can conclude that 40-50% of children receiving Btx respond positively to the injections with decreases in ankle tone and equinus during gait. This value is similar to that observed by Boyd et al. (2000) and Koman et al. (2000) who estimate that 50-60% of children with cerebral palsy respond to this treatment.
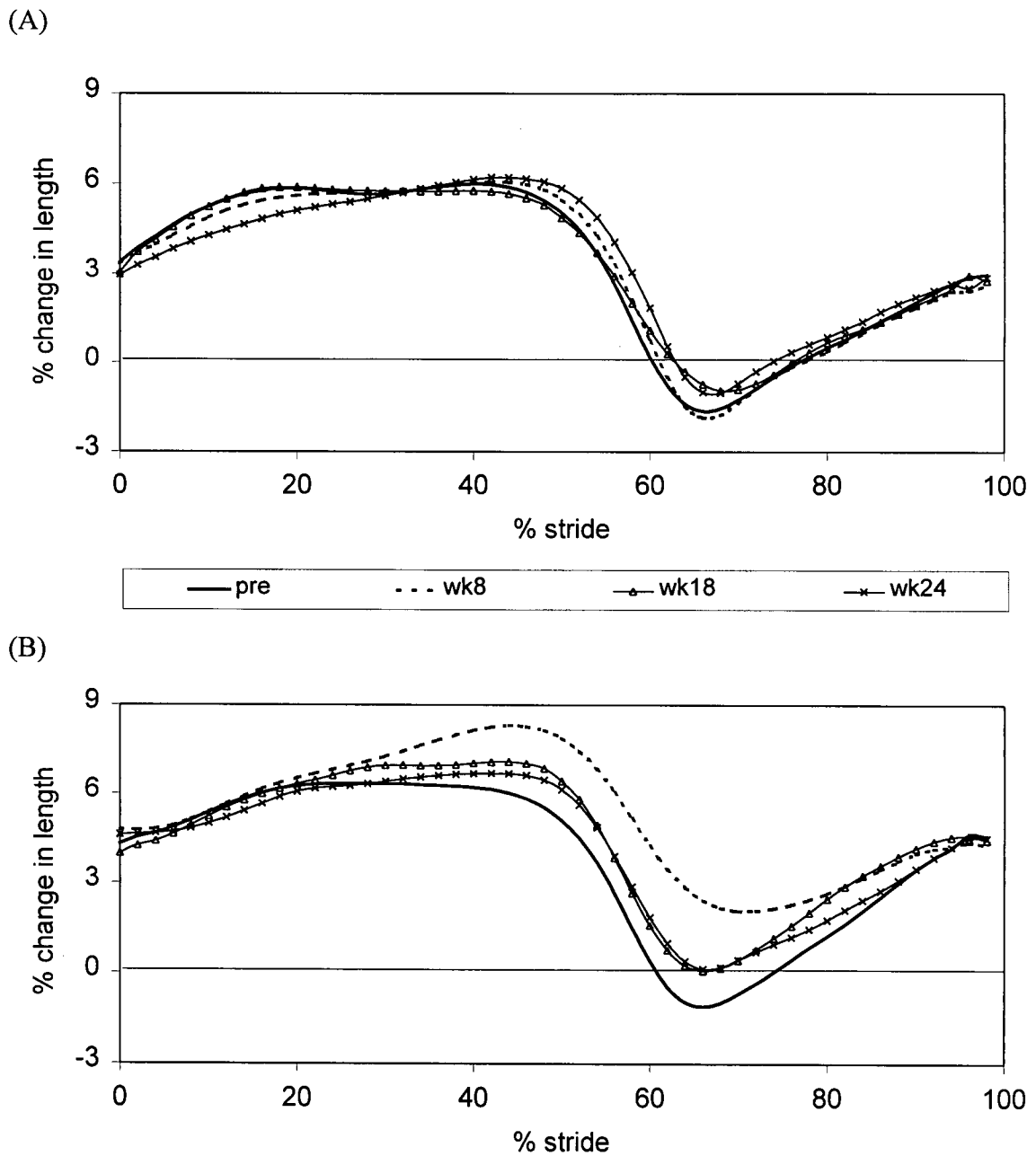
(A)



(B)



*Figure 2.4.3-2: (A) Mean calculated gastrocnemius muscle length during one stride of the 5 subjects (10 limbs) recieving Btx injections before- and at 8, 18, and 24-weeks post-injection. (B) Mean calculated gastrocnemius muscle length during one stride of the 3 subjects (6 limbs) revieving both Btx and serial casting before and at 8, 18, and 24-weeks post-injection.*

Koman et al. (2000), measuring the M-response after supramaximal stimulation of the posterior tibial nerve, has estimated that Btx partially denervates the gastrocnemius/soleus complex by approximately 20%. Taking into consideration that only the medial and lateral heads of the gastrocnemius were injected with Btx and that approximately 40% of plantarflexor torque comes form the gastrocnemius muscle alone (Cresswell, Loscher, and Thorstensson, 1995), with maximal activation, only 8% of the gastrocnemius would have been denervated. During walking, the ankle plantarflexors are far from maximally activated, therefore the slight decrease in force-generating capacity of the injected muscle is most likely not significant enough to allow for a decrease in equinus during gait. Olney et al. (1990) has reported that in spastic limbs, the ankle plantarflexors produce just over a third of the positive work for walking, as opposed to 75-80% in normal limbs. In addition, measurement of the M-response is taken with the patient lying in a supine position with unloaded joints. During walking, evidence suggests that there is increased spasticity while standing due to the low tone activation of antigravity muscles to maintain standing balance (Perry, 1993). Perhaps the finding that in the Btx only group decreases in ankle plantaflexor tone measured by the Modified Ashworth Scale with the ankle and knee joints in isolation do not correspond to decreases in ankle equinus during gait are due to this phenomenon.

The majority of studies reporting the positive effects of Btx injections on gait have been using Physician Rating Scales (PRS) (Corry et al., 1998; Koman et al., 2000; Wong, 1998). Unfortunately, as reported by Corry et al. (1998), the reliability of this rating scale is questionable. Substantial agreement was only found with the footstrike category of the PRS (Corry et al., 1998). The remaining 3 sections only had slight-to-moderate agreement. An expanded version of this rating scale is used in the multi-centre trial carried out by Koman et al. (2000) with no mention of overall reliability. At this time, the lack of test-retest reliablility questions the use of the PRS for gait assessment in this population of children, especially since only minimal improvements in gait are observed using the more objective tool of gait analysis.

Because we did not include a group of patients receiving only serial casting as a treatment, we cannot discount that the improvements in gait of the combined treatment group were the result of casting alone. For those subjects who received the combined treatment of Btx in addition to serial casting, 2 subjects (4 out of 6 legs) had a measurable decrease in plantarflexor tone as measured by the Modified Ashworth Scale at both the 8 and 18 week testing sessions. The one subject who had no decrease in tone after treatment had a score of 1 in both before treatment and therefore could only have a measurable decrease in tone if the spasticity was removed completely. All three of the subjects who received both Btx and casting had increases in passive and dynamic ankle dorsiflexion and corresponding increases in gastrocnemius and soleus length during gait. At 24 weeks post-injection, although ankle plantarflexor tone was decreased over baseline in only 1 subject (both legs), increases in passive ankle dorsiflexion and ankle dorsiflexion during gait were still present along with increases in ankle plantarflexor length. In Corry et al.'s casting only group, improvements in ankle dorsiflexion during gait had returned to baseline values by 12 weeks after cast-removal (the 18 week assessment in this study). That improvements are still evident at the 24 week assessment leads to the possibility that the positive effects were due to the combination of Btx and casting and not attributable to casting alone.

Boyd et al. (2) has recently stated that the ideal candidate for Btx therapy is aged 2-4 years with a purely dynamic equinus. Furthermore, Cosgrove et al. (6) reported an age related Btx effect with younger patients having increased maximum dorsiflexion during gait than older patients. Due to constraints in measuring the gait of younger subjects, only the gait of patients older than 4-5 years of age has been evaluated after Btx injections. These children have an increased liklihood of fixed ankle plantaflexor contractures and therefore are less likely to be responsive the Btx. Using the combination of casting and Btx has the potential to be effective in all of these children as it lengthens the muscle in addition to decreasing the muscle tone. Btx decreases tone and cannot lengthen the muscle.

Examination of group results revealed that the combined treatment of serial casting and Btx did have more persistent effects than Btx alone in improving ankle plantarflexor tone and ankle equinus measured passively and during gait. It can be concluded that combining both Btx and serial casting appears to have a higher success rate than Btx alone, possibly because in addition to the lengthening of the muscle, the force-generating capacity of that same muscle is decreased. Additional studies with increased subject numbers using more objective outcome measures are needed in this area to validate the effect of combining Btx with serial casting for treatment of ankle equinus.

## 2.6 ACKNOWLEDGEMENTS

# CHAPTER 3: CONCLUSIONS AND FUTURE DIRECTION

## 3.1 CONCLUSIONS

The purpose of this study was to investigate if the combined treatment of Btx and casting led to more persistent improvements in ankle plantarflexor spasticity, passive ankle movement, motor functioning, gait, and muscle lengths than Btx alone.

Examination of group data reveals that the combination of Btx and serial casting does lead to more persistent improvements in the parameters investigated than Btx alone. Both groups did respond to treatment, even though improvements in the Btx only group were limited to subjective measures. Because only 2 of 5 subjects in the Btx only group responded to the treatment, data were investigated on a case-by-case basis. These data revealed that in these two patients, improvements in spasticity, passive ankle range of motion, gait parameters, and muscle lengths were improved through 18 weeks post-injection. Because these two subjects were not able to complete testing at 24 weeks, it cannot be determined if improvements were still evident at that time.

The combination of Btx and serial casting appears to be a more effective treatment for ankle equinus than Btx alone as it was effective in all subjects compared to just 2 out of 5 in the Btx only group. It is postulated that this is because the combination affects both the force-generating capabilities as well as the rheologic properties of the muscle.

## 3.2 RECOMMENDATIONS FOR FUTURE WORK

The current literature investigating the use of Btx as a treatment for spasticity in cerebral palsy lacks standardization and consistency. In the majority of published studies, the dosage of Btx injected varies greatly between studies and even within studies. Surprisingly, an inconsistent number of injections are given and various muscles are

injected within the same study. In addition, most studies rely on subjective tools to document the positive effects of Btx, few report positive results obtained with the use of objective tools such as gait analysis.

In this study, the unfortunate lack of a casting only treatment group made interpretation of the results somewhat difficult. The lack of subject numbers participating in this study also hindered the results. An objective measure of ankle plantarflexor spasticity was attempted; however, the results were disappointing.

In light of the recently reported efficacy of Btx in this population being only 50-60%, studies relying on more objective measures and consistent protocols are essential to determine how beneficial Btx is as a treatment in cerebral palsy. This study needs to be repeated with a group receiving only serial casting and with subjectis who respond to the Btx. A comparison between casting and night splints combined with Btx would be beneficial to determine if similar effects can be elicited without the inconvenience of casting.

# APPENDIX A: LITERATURE REVIEW

## A.1 CEREBRAL PALSY

Cerebral Palsy refers to a group of disorders of the central nervous system manifested by aberrant control of movement or posture and are not the result of recognized progressive disease (Nelson and Grether, 1999). More specifically, cerebral palsy is a non-progressive motor disorder secondary to finite central nervous system insult, usually occurring before, during, or shortly after birth, characterised by an inability to fully control motor function, particularly muscle control and coordination. No cure exists, nor is one imminent.

Most children will also have other disorders, with the likelihood of these disorders increasing with a greater degree of spasticity increasing limb involvement (Eicher and Batshaw, 1993). Additional disabilities attributable to CNS damage include cognitive impairment, loss of vision or hearing, seizures, communication and behavioural disturbances, and chronic systemic problems of the gastrointestinal system, respiratory system and musculoskeletal system (Eicher and Batshaw, 1993).

### A.1.1 Epidemiology

The incidence of cerebral palsy remains at approximately 2 per 1000 live births (Mutch et al., 1992; Rosen and Dickinson, 1992). Although the incidence of cerebral palsy has not changed, the profile has. Because of the higher survival rate of low birth weight infants, the incidence of spastic diplegia has increased to as much as 50% of those born each year with cerebral palsy (Krageloh-Mann et al., 1995).

### A.1.2 Classifications

Cerebral Palsy can be grouped into 4 main categories (Mutch et al., 1992): spastic, athetoid, ataxic, and mixed. This Swedish classification system addresses both the movement disorder and it distribution (Ingram, 1984; Mutch et al., 1992).

Spastic cerebral palsy accounts for approximately 70% of all cases. Spastic CP is due to upper motor neuron involvement and the child may have mildly or severly affect motor function. Spastic CP can further be divided into 4 major types. Spastic hemiplegia occurs when there is involvement of both limbs on one side of the body. The arm is usually more affected than the leg. Spastic paraplegia is characterised by involvement of both legs with relative or complete sparing of the arms. Quadriplegia or tetraplegia has involvement of all limbs to a similar degree. Spastic diplegia, the most common form of spastic CP, is considered to be a form intermediate to paraplegia and quadriplegia. Spastic hemiplegia and spastic diplegia have the best prognosis for functional recovery (Nolan et al., 2000).

In spastic diplegia, the legs maintain greater spasticity and weakness than the arms. These children usually have periventricular leukomalacia as the pathological substrate. Children with spastic diplegia exhibit upper motor neuron signs such as weakness, hypertonicity, hyperreflexia, clonus, pathological reflexes (eg., extensor plantar response), and a tendency for contractures at the foot and ankle.

Athetoid cerebral palsy comprimises approximately 15% of all cases and is usually characterised by involvement of the basal ganglia. The result is slow, writhing, involuntary movements that affect the extremities (athetoid) or the proximal parts of the limbs and trunk (dystonic). Abrupt, jerky, distal movements (choreiform) may also be present. These movements increse with emotional tension and are not present during sleep. Dysathria is present and often severe.

Approximately 5% of children with CP are ataxic with cerebellar involvement. Weakness, incoordination, and intention tremor produce unsteadiness leading to a wide-base gait and extreme difficulty with fast or fine movements.

The rest of children diagnosed with cerebral palsy are not easily classified into one of the above groups and are considered to have a mixed form of cerebral palsy. The most common combination is spasticity mixed with athetosis.

*A.1.3 Causes*

Many factors, both acquired and genetic, may result in a variety of peripheral manefestations that collectively are referred to as cerebral palsy. Hypoxic-ischemic injury, structural malformations, vascular disorders, intraventricular or subarachnoid hemmorage, infections (both maternal and fetal), hormonal disorders, toxins, trauma, metabolic disease (including autoimmunity and inflammation), prematurity, and hemolytic disease of the newborn (Nelson and Grether, 1999). There is also a higher risk of CP in multiple births, usually related to associated prematuriy or to antenatal death of one twin or triplet (Pharoah, 1996; Van Heteren et al., 1998). There is a history of prematurity in approximately 50% of children born with CP (Blasco, 1992; Kuban and Leviton, 1994).

The newborn with spastic cerebral palsy exhibits periventricular leukomalacia and periventricular hemorrhagic infarction (Okumura et al., 1997). Periventricular leukomalacia consists of symmetrical, focal necrosis of the white matter dorsal and lateral to the external angle of the lateral ventricles. Diminished myelin and dilated lateral ventricles, or more seriously, cyctic cavities develop. Because the descending motor fibres from the cortex to the lower extremities are closest to the ventricle, these lesions most commonly result in spastic diplegia. Periventricular hemmhoragic infarction consists of asymmetric hemmorhagic necrosis of the periventricular white matter with an associated germinal matrix or intraventricular hemmorhage. The common clinical manifestation is spastic hemiperesis as these lesions tend to involve the descending tracts to both the arm and leg. The pathological mechanisms for both these types of injury remains uncertain, but may involve a cascade of events that includes hypoxia, ischemia, vascular sensitivity, maturational vulnerability of neurons, autoregulation dysfunction, glutamate receptor development, and specific metabolic properties of cerebral regions or cell types.

A.1.4 *Manefestation*

All children with cerebral palsy have impaired coordination of muscular activity making normal movement and postural control difficult, sometimes impossible, to achieve. For patients with spastic diplegia, muscle hypertonicity, abnormal timing and recruitment of muscles, weakness, reduced equilibrium, and reduced joint motion or joint deformity due to dynamic and static muscle contractures contribute to their impaired mobility and increased energy consumption (Gage, 1991; Rose, Ralston, and Gamble, 1994; Damiano and Abel, 1998). Depending on the site and extent of the brain injury, these peripheral manefestations occur either singuarly or in combination (Koman et al, 1994). Decreased joint range of motion in the lower limb as a consequence of the spasticity is the most recorded and noticeable impairment (Cosgrove et al., 1994; Abel and Damiano, 1999; Koman et al., 2000).

The exaggerated and excessive contraction of spastic muscles initiated by abnormal stretch reflexes secondary to pyramidal or extrapyramidal lesions occur in a specific pattern. These patterns result from spasticity on one side of the joint with relative hypotonia/weakness on the other side. The spasticity may create a dynamic deformity sufficient to interfere with function (patient positioning, hygiene, sitting balance, independence of activities of daily living, and ambulation). In the lower extremity, imbalance results most frequently in varying degrees of hip flexion and adduction deformity, knee flexion, and ankle plantarflexion (equinus). Over time, these sustained imbalances of spasticity-induced joint positioning result in further shortening of the spastic/agonist muscle and an increase in the resting length of the relatively hypotonic or antagonist muscle groups with subsequent further weakening (Koman 1994). These changes in turn result in further imbalances that lead to dynamic joint contractures and if full range of motion of the joint is not maintained by active motor power or passive assistance, fixed contractures and/or bony deformities will result.

*A.1.5 Motor development in children with cerebral palsy*
Motor development does occur in children with cerebral palsy, but it does not follow the normal timing. Children with cerebral palsy exhibit a delayed acquisition of motor skills such as independent stance and walking (Bennett, 1987) possibly due to poor balance

control (Bleck, 1994). These children retain some of the characteristics seen in infants (Leonard et al., 1991).

### A.1.6    Balance

Balance is essential for upright posture and independent walking. The ability to control posture is developed early in life and includes more stability in different sensory conditions, more organised muscle reponses to external perturbations, and better feed-forward control (Haas et al., 1989; Woollacott and Sveistrup, 1992). Children with cerebral palsy have a delayed emergence of locomotor and manipulative skills due to the delayed development of postural control to support these activities (Woollacott and Burtner, 1996).

Studies on the development of postural responses to unexpected balance pertubations show a clear developmental progression of the emergence of muscle responses in children. In normal children, there is a sequential development of neuromuscular responses that control balance (Woollacott and Burtner, 1996). In children less than 8 months of age (the time of acquisition of the "pull-to-stand" behaviour) there is no coordinated muscle response organisation when balance is disturbed. In children greater than 8 months of age, when they have acquired "pull-to-stand" behaviour, there are directionally appropriate muscle responses to balance disturbance. As the child gains standing and walking experience, additional agonist muscles are added to the response pattern and a consistent distal to proximal sequence begins to emerge. The antagonist muscle coactivation typically seen in younger children is reduced as postural control becomes refined by about 15 months of age (Forssberg and Nashner, 1982; Shumway-Cook and Woollacott, 1985).

Children with cerebral palsy have different balance responses than typically developing children. In the pull-to-stand stage, children with CP and typical children are very similar in the neuromuscular components of balance as muscle responses are not yet well organised (Woollacott and Burtner, 1996). Studies examining the development of postural control in children with spastic diplegia have shown that older children with

cerebral palsy have muscle activation patterns typically seen in normal children who are at the pull-to-stand stage of development or are inexperienced walkers (Nashner, Shumway-Cook, and Marin, 1983; Wollacott and Burtner, 1996; Burtner, Qualls, and Wollacott, 1998). Children with cerebral palsy still exhibit increased recruitment of antagonist muscles (coactivation), a reversal of muscle recruitment (proximal to distal ordering of muscle onsets), and a decrease in trunk muscle activity. Typical children at this stage recruit muscles in a distal to proximal fashion with little or no coactivation resulting in the smoothing of the postural response (Woollacott and Burtner, 1996).

A number of neuromuscular factors have been hypthesized to contribute to these balance difficulties common in children with cerebral palsy (Crenna and Inverno, 1994): defective recruitment of motor units; abnormal velocity-dependent recruitment during muscle stretch (i.e. spasticity); nonselective activation of antagonist muscles; interference of immature or nonpertient motor programs; and changes in the passive mechanical properties of muscle itself. These neuromuscular factors lead to musculoskeletal constraints including crouched posture that also contribute to the lack if balance flexibility and control.

Wollacott and Burtner (1996) investigated the effect of musculoskeletal limitations on muscular responses to standing balance perturbations. Having control subjects stand with a crouched posture similar to that seen in children with spastic diplegia (i.e. flexed hips and knees and plantarflexed ankles) caused postural muscle response patterns to approximate more closely those of children with spastic diplegia. There was an increase in antagonist muscle activity with cocontraction and the muscle onset latencies were similar to those of children with cerebral palsy. These investigators concluded that body alignment is an important factor contributing to muscle response characteristics. This finding suggested that the neuromuscular response seen in children with spastic diplegia may be appropriate for their musculoskeletal constraints.

The visual, somatosensory, and vestibular systems are the primary source of sensory information providing the central nervous system with different modalities of information

about the individuals position and movement. Normally, information from these sources is consistent and redundant, but if these inputs are not consistent, the individual must determine the most accurate source of information to appropriately maintain balance (Forssberg and Nashner, 1982; Shumway-Cook and Woollacott, 1985). The ability to integrate sensory information appropriately is refered to as sensory integration (Shumway-Cook and Woollacott, 1985) or sensory organisation (Nashner, Shumway-Cook, and Marin, 1983). Cherng et al. (1999) compared static standing balance in children with cerebral palsy to age-matched controls under altered sensory conditions. They concluded that children with spastic diplegia tend to rely on somatosensory information for maintaining standing balance and have difficulty switching their dependance from unreliable somatosensory information to other types of reliable sensory input (Cherng, 1999). Either the children with cerebral palsy have difficulty reweighing their dependence to vestibular information or their vestibular information is innacurate.

Poor standing balance may be the result of an inability to produce appropriate motor output, a deficient ability to organize sensory information, or simply an incapacity to stand upright, not in a crouched posture. It is most likely a combination of all three of these factors.

### A.1.7 Gait

At the same time that postural standing balance is maturing, the child's walking performance is also developing. The development of locomotion is a two stage process: (Bril and Breniere, 1993), learning to control balance (first 3-5 months of independent walking) and the progressive refinement of the locomotor pattern (5 months to 4 years walking experience). During the first 3-4 months of walking there is a rapid decrease in the double support phase of gait, and increase in step length and a decrease in step width all of which relate to the mastery of balance control.

Newborn stepping movements of human fetuses, anencephalic infants, and normal infants directly after birth support the existence of spinal-cord locomotor generating patterns or central pattern generators (Leonard et al, 1991). These stepping movements produced by

antagonist coactivation of leg muscles during ground contact of the feet disappear in normal infants by about 10 weeks. At about 8 months of age, locomotion reappears as supported walking. By 12 months of age, most children can walk independently and do not require support. It is not until the child is in his or her third year of life that adult gait features, such as a prominent heelstrike, knee flexion during stance, asynchronus joint movement, and specific muscle activation patterns emerge (Saunders, Inman, and Eberhart, 1953; Forssberg, 1985). The period of supported walking and the beginnings of independent gait is characterised by coactivation of antagonist leg muscles, a low and poorly modulated exensor EMG activity, and a short-latency stretch reflex of the gastrocnemius at the start of stance phase (Berger, 1998). These characteristics are most likely a mechanism to support the body for equilibrium control (Berger et al., 1992).

There has been numerous theories proposed about the processes involved in the development of human gait. In 1987, Thelan and Cooke put forward a theory having to do with muscle strength and limb dynamics. Zelazo (1983) proposed that higher cerebral functioning, or cognition and motivation, was responsible for the maturation of human locomotion. Neural remodelling of supraspinal systems (Forssberg 1985) and of the transcortical pathways (Dietz, 1987) has also been considered. The most prominent of these theories is neural remodelling.

The deficits in locomotion in children with cerebral palsy has been studied extensively by Leonard and colleauges (1990, 1991) and Dietz and colleagues (1984a, 1984b, 1987, 1990). Leonard et al. (1991) concluded that as a child with cerebral palsy matures, he or she retains some of the characteristics of this infant locomotor pattern, suggesting that the sensorimotor cortex is involved in the development of normal gait patterns. Supporting the concept of deficient supraspinal influences, Leonard et al., (1990) found a lack of reciprocol inhibition before voluntary movement in children with cerebral palsy. Dietz et al. hypothesize that the maturation of EMG responses during gait is achieved by the establishment of afferent and efferent control of locomotor activity (Dietz, Quintern, and Berger, 1984a, 1984b; Berger, Quintern, and Dietz, 1987).

In addition, the response to brain damage depends on the stage of development of the nervous system at the time the damage occurs (Levay, Wiesel, and Huber, 1980; Stanfield, O'Leary, and Fricks, 1982; Goldberger, 1988). The gait pattern of adults who have suffered damage to the sensorimotor cortex is considerably different than that of children with cerebral palsy (Berger, Quintern, and Dietz, 1982). Adult patients with spastic hemiparesis or paraperesis maintain reciprocol antagonist activation of the leg muscles which indicated intact central programming once established (Berger, 1998). Children with cerebral palsy have a coactivation of leg muscles, suggesting that the maturation of the normal gait pattern has not yet been established and normal development has not taken place. The gait pattern of children with cerebral palsy resembles that of normal children in the stage of supported walking or the earliest stage of independent walking (Berger, 1998). It appears as if the movement deficit observed in children with cerebral palsy is due to a lack of development of the central nervous system and its repercussions.

*A.1.8   Abnormal gait in children with spastic diplegia*

Children with cerebral palsy have difficulties with ambulation due to some or all of the following: loss of selective muscle control, dependence on primitive reflex patterns for walking, abnormal muscle tone, relative imbalance between agonists and antagonists across joints, and deficient equilibrium reactions (Gage, DeLuca, and Renshaw, 1996). Since selective motor control becomes more deficient as one moves distally, control of trunk and proximal joints is much better than that of distal joints (Gage, 1991). As such, it is the ankle and knee joints that are usually more affected, and since the knee and ankle are crucial in locomotion, treatment is aimed at these joints.

In children with spastic diplegia, the ankle is most often in an equinus position due to spasticity of the triceps surae muscle group. This results in inappropriate internal muscle moments that interfere with stability in the stance phase of gait. In first rocker, the heel contacts the floor and acts as the fulcrum as the foot is lowered to the ground under eccentric control of the ankle dorsiflexors. At heelcontact, an internal plantarflexor moment due to spasticity causes the foot to land flat or in an equinus position instead of

with the heel. First rocker, then, ceases to exist as there is no heel contact. During second rocker, the tibia progresses over the base of support (foot) causing the ankle to dorsiflex under eccentric control of the triceps surae muscle group. When the ankle plantarflexors are spastic, this movement is restrained as the vertical ground reaction force passes anterior to the knee, resulting in an excessive extension moment of the knee. One of two adaptations will take place because of the biarticular role of the tricep surae (due to the gastrocnemius muscle). Either the knee will hyperextend or there will be premature heelrise and the child will bear the weight on his or her toes instead (i.e. early progression to third rocker, where the fulcrum is the MTP joints). In third rocker, when the fulcrum is the MTP joints, the plantarflexors contract concentrically to propel the body forward. When these muscles are spastic, the internal muscle moment is too large causing the knee to remain extended which results in the body being propelled more upwards than required. Alternatively, if there is an inadequate muscle moment produced by the triceps surae muscle group in third rocker, there will be a persistent crouch and the hip flexors will pull the limb into swing instead of the ankle plantarflexors. The net result of this action is that more energy is consumed.

## A.1.9 Treatments for spastic equinus

The ability to walk is a major concern for parents. Improving or maintaining this ability while simultaneously inhibiting the influence of abnormal muscle tone and reflex patterns are often considered to be the primary focus of most therapeutic interventions addressing the motor deficits in these children.

Muscle-tendon lengthening is often performed on children with contractures of the ankle plantarflexors to facilitate walking and normal growth and development (Bleck, 1987). Because growth and maturation factor into the outcome, less invasive methods are attempted in order to delay surgery (Rattey et al., 1993). Two such treatments that are commonly used to delay surgery are serial casting and botulinum toxin injeciton (Btx).

**A.2 SERIAL CASTING**

Serial casting is a conservative treatment for ankle equinus resulting from contracture. The ankle joint is immobilized with the triceps surae subjected to stretch. The casts maintain a joint in a functional position and are used to decrease the effects of tone and to increase functional movement. The overall goal of serial casting is to postpone surgery until growth and maturation no longer factor into the outcome.

*A.2.1 Benefits*

The primary benefit of serial casting is to increase the length of the spastic triceps surae muscle group. Secondarily, serial casting acts to return ankle motion to a more normal range (i.e. decrease ankle equius). Serial casting is reported to supress tonic stretch reflexes (spasticity) (Bishop, 1977; Cusick & Sussman, 1982; Zachezewski, 1982; Duncan and Mott, 1983; Barnard et al, 1984; Carlson, 1984), improve passive ankle dorsiflexion (Watt et al, 1986; Corry et al., 1998; Flett et al., 1999), and facilitate developmental motor skills such as standing and walking (Sussman, 1983; Jordan, 1984). The gait of children receiving serial casts is temporarily improved after removal (Corry, et al., 1998; Flett et al., 1999). Serial casting is reported to prevent excessive ankle plantarflexion and normalize lower-extremity muscle timing (Carlson, 1984), normalize movements of the trunk, pelvis, hip, knee, and ankle (Cusick and Sussman 1982; Duncan and Mott 1983; Hylton 1990), improve foot floor contact (Watt et al, 1986), and increase stride length (Bertoti 1986; Hinderer et al., 1988). Serial casting postpones the liklihood of fixed contractures occurring in the triceps surae muscle group by lengthening the muscles and allowing a more normal range of motion at the ankle joint.

*A.2.2 Mechanism of action*

Serial casting is reported to induce both a reflex response and a mechanical response. Prolonged muscle stretch reduces the amplitude of the H-reflex through autogenic inhibition from secondary spindle endings (Burke et al., 1971) and is believed to contribute to the reduction of dynamic reflex responses (Tremblay, 1990). Otis (1985) suggested that immobilization decreases the static and dynamic stretch sensitivities as

the intrafusal fibres adapt to the increased length of the extrafusal fibres. The increase in length of the muscle fibres results in spindle afferents being unloaded at a given ankle position, contributing to reduced spasticity (Gage, 1991)

The mechanical stretch induces muscle lengthening through the serial addition of sarcomeres in the muscle fibres (Williams and Goldspink, 1971). Immobilizing muscle in stretched position extends the sarcomeres to a length where there is a less than ideal overlap of myofilaments for maximal tension to be developed (Williams and Goldpsink, 1978). Increasing number of sarcomeres restores optimal overlap and the length tension properties of the muscle are not altered (Tabary et al 1972a; Tabary et al., 1972b; Tardieu C et al. 1982). When a musculo-tendinous unit experiences permanent elongation of the series elastic component as a result of being maintained at a length greater than its resting length, it can be expected that both the dynamic and static sensitivities will be altered at a given joint position (Otis, 1985). There will be a decrease in static sensitivity because it will require less external effort to hold the ankle in a given position and there will be a decrease in dynamic sensitivity as the joint functions in a relatively more dorsiflexed position.

In feline studies, muscle lengthening persists for 4 weeks after cast removal after which time the number of sarcomeres in series gradually returns to pre-casting levels (Tabary 1972a; Tabary et al., 1972b; Goldspink et al., 1974). In studies examining the longterm effects of serial casting on children with cerebral palsy, improvement in ankle dorsiflexion during gait lasts up to 12 weeks after cast removal: ankle motion returns to pre-casting range by 12 weeks (Corry et al, 1998).

## A.3   BOTULINUM TOXIN

The goals of treatment in children with cerebral palsy are to maximize function and minimize the secondary effects of the affliciton, such as joint contracure and other musculoskeletal malformations, by promoting longitudinal muscle growth (Reimers, 1990; Cosgrove, Corry, and Graham, 1994), to delay or prevent orthopedic surgical

intervention (Koman et al, 1993; Russman Tilton, and Gormely, 1997; Koman et al., 2000).

Botulinum toxin (Btx) is indicated for treatment in children with cerebral palsy when spasticity is interfering with function (Koman et al., 1993). Early therapeutic treatment is indicated as early childhood is the key time in the development of motor skills. The most common indications for Btx administration in this population are: (a) dynamic ankle equinus, with the goal to reduce spasticity and to improve gait; (b) adductor spasms, with the aim to reduce scissoring or to improve hygeine; and, (c) upper limb spasticity, with the aim to attain functional or aesthetic improvements (Bentavoglio, 1999).

In this population, Btx is reported to decrease spasticity/tone by partially denervating the injected muscle, promote muscle balance across joints, increase range of motion at the treated joint, and improve ambulation (Koman et al., 1993, 1994; Calderon-Gonzales, 1994; Cosgrove et al., 1994; Flett et al., 1999; Sutherland et al., 1999; Koman et al., 2000). Motor functioning may also be enhanced (Flett et al., 1999).

### A.3.1   What does it do?

Btx reduces the effects of spasticity by decreasing the total force produced by the injected muscle (Forssberg and Tedroff, 1997). The H-relex is not affected (Koman et al., 2000). When injected intramuscularly in therapeutic doses, it produces a partial chemical denervation of the muscle resulting in localized muscle paralysis. Some degree of muscle tension is maintained as not all muscle fibres are affected. It is also reported to decrease coactivation (Bentavoglio, 1999).

In the absence of fixed deformity or rigid joint contracture, Btx can be used to restore across-joint muscle balance by diminishing the effects of spasticity in agonist muscle, thereby facilitating and improving function of the previously weakened and lengthened antagonist muscles. Potential secondary gains are prevention of joint contracture or fixed deformity and alteration of the natural history of the specific motor deficit (Bentavoglio and Albanese, 1999). Btx cannot correct underlying etiological factors involved in

spasticity or cerebral palsy nor can it directly imporve function or performance. It can delay surgery until the effects of growth and maturation have a diminished effect on the outcome (Cosgrove et al., 1994; Boyd et al., 2000).

### A.3.2 What is it?

Botulinum toxin is produced by the gram-negative, rod-shaped anaerobic bacterium *Clostridium botulinum*. There are seven antigenically different serotypes (A-G) and the bacteria that produce these serotypes are given the same designations. Only A, B, E, and F cause human botulism (Tsui, 1996) and A is the most commonly used therapeutic botulinum toxin as it is the most potent (Sellin, Kauffman, & DasGupta, 1983; Sellin, Thesleff, & DasGupta, 1983; Tsui, 1996).

### A.3.3 Discovery of Botulinum Toxin (aka the sausage poison)

Botulism, a form of food poisoning caused by ingestion of Btx, is characterised by general muscle weakness which first affects ocular and throat muscles and extends later to all skeletal muscles. In more severe forms, there is general flaccid paralysis, impairment of respiration and autonomic functions and eventually, death from respiratory failure. The World Health Organization estimates that more than 450,000 infants in 1991 died as a result of botulinum poisoning (Whitman et al., 1992). The most common source - food intoxication (Montecucco and Schiavo, 1995).

The first accurate and complete description if the clinical symptoms of food-borne botulism was published by the German physician Justinus Kerner (1786-1862) between the years 1815-1822. He also hypothesized that the toxin, once identified, could have a therapeutic use.

In the early 1800's, there was a dramatic increase in the cases of fatal food poisoning throughout Germany attributed to the rise in poverty and decline in hygienic measures for rural food production after the devastation of Napoleonic warfare. In July 1802, the German government on Stuttgart issued a public warning about the harmful consumption

of smoked blood-sausages. In 1811, "sausage poisoning" was believed to be caused by prussic acid. Medical Faculty at the University of Tubingen were asked for advice. Wilhelm Gottfried von Ploucqet (1744-1814) disputed that prussic acid was the toxic agent in sausages, suspecting a biological poison (Erbguth and Naumann, 1999). Johann Heinrich Ferdinand Autenrieth (1772-1835) then studied reports from general practitioners and health officers on cases of food poisoning and issued a list of symptoms from "sausage poisonoing" which included gastrointestinal problems, double vision, and mydriasis. He also suggested that housewives should be blamed for the poisoning because they did not boil the sausages in water long enough (Erbguth and Naumann, 1999).

At the same time, Justinus Kerner, a medical officer in a small town in Germany, observed cases of lethal food poisoning and published his forst monograph in 1820 on sausage poisoning (Erbguth and Naumann, 1999). He summarized the case histories of 76 patients andgave a complete clinical description of what it now recognized as botulism. He moved to Weinsberg and conducted research on the sausage poison. In 1821, he began experimenting on animals and himself, beleiving that the toxin was a fatty acid. In 1822, his second publication described the results from his animal studies and contained the clinical evaluation of 155 case reports of food poisoning including post-mortem studies (Erbguth and Naumann, 1999). Kerner deduced that the toxin acts by an interruption of the signal transmission within the peripheral and the sympathetic and parasympathetic nervous system, leaving the sensory signal transmission intact (Erbguth and Naumann, 1999). In his postmortem studies, he determined that the cause of death was secondary respiratory and cardiac failure. Kerner concluded that (a) the toxin develops in bad sausages under anaerobic conditions, (b) the toxin acts on the motor and autonomic motor systems, and (c) the toxin is strong and lethal even in small doses and suggested that sausages should be adequately cooked.

Kerner also developed the idea that the toxin could be used for therapeutic purposes. He concluded that the toxin, in small doses, could decrease the hyperactivity of the nervous system. He postulated that the toxin could be used for some movement disorders as well

as for hyperexcretion of body fluids (sweat and mucous), ulcers form malignant diseases, skin alterations after burning, delusions, rabies, plague, consumption from long tuberculosis, and yellow fever (Ergbuth and Naumann, 1990). Today, the toxin is used in many of these cases.

Kerner became known as "Wurst-Kerner" ("Sausage-Kerner"). In 1870, the sausage poison was named *botulism*, form the Latin name for sausage, "bolulus". The discovery of the true nature of the toxin came in 1895, when microbiologist Emile-Pierre van Ermengem determined that bacteria produced the toxin after investigating an outbreak of botulism following a funeral ceremony. It wasn't until 1949 that botulinum toxin was discovered to block neuromuscular transmission, laying the foundation for its development as a therapuetic tool (Burgen, Dickens, and Zatman, 1949).

There is no known cure for the paralysis caused by the toxin. Preparations of antitoxin are available but by time clinical symptoms are present, toxin has irreversibly bound to the cholinergic nerve terminals blocking acetylcholine release (Hambleton, 1992). Treatment at this stage will not reverse or relieve existing symptoms but neutralize any unbound toxins.

*A.3.4 Mechanism of action*

Btx acts presynaptically by blocking the release of neurotransmitter acetylcholine at the neuromuscular junction. The toxin produces a concentration-dependent blockade of acetylcholine exocytosis at he presynaptic cleft. Botulinum toxins are synthesized as inactive single-chain polypeptides with a molecular weight of 150,000 daltons. The toxin becomes active when it is nicked by proteolytic enzymes to give a dichain molecule. The active Btx molecule is composed of a heavy chain (100,000 daltons) linked by a dispulphide bond to a light chain (50,000 daltons) that is associated with one molecule of zinc (Schiavo et al., 1992). The heavy chain determines cholinergic specificity and is responsible for binding to the nerve cell while the light chain is the intracellular toxic moiety (Simpson, 1989; Coffield, Considine, and Simpson, 1994).

Three stages are involved in the inhibition of acetylcholine: a primary step in which the toxin binds rapidly and irreversibly to acceptors on the presynaptic nerve surface; an internalization stage in which the toxin crosses the plasmalemma and enters the nerve terminus; and the final step involving the disabling of the acetylcholine release mechanism (Simpson, 1981; Brin, 1997).

Toxin Binding: The toxin molecule binds to the presynaptic membrane at the neuromuscular junction of alpha-motor neurons (Black and Dolly, 1986b). The heavy chain is responsible for toxin binding (Valtorta, 1993). The toxin binds rapidly and irreversibly to uncharacterized receptors on the presynaptic nerve surface (Black and Dolly, 1986a; Habermann and Dreyer, 1986). Dolly et al. (1984) have estimated there to be approximately 150-200 binding sites/$\mu m^2$ of membrane and it appears as if the receptors are located in all unmyelinated areas of murine motor nerve terminals.

Internalization: Once the toxin has attached itself to the membrane, it enters the nerve terminus by an energy-dependent process (Dolly et al., 1984). This process resembles that of receptor-mediated endocytosis whereby molecules are encapsulated in clatherin-coated endosomes whose internal environment becomes acidic as they progress in to the cytosol (Hambleton, 1992). At low pH, BTX undergoes a conformational change from a water-soluble "neutral" form to an "acid" form, characterised by the exposure of hydrophobic segments (Boquet and Duflot, 1982). This hydrophobicity enables the penetration of both the L and H chains in to the hydrocarbon core of the lipid bilayer, with the L chain continuing into the cytosol after the disulphide bond is broken (Boquet and Duflot, 1982). Because nerve stimulation facilitates intoxication (Hughes and Whaler, 1962), botulinum toxins appear to be taken up at the neuromuscular junction inside small synaptic vesicles or other vesicles whose recycling is linked to synaptic activity. This process is energy dependent (Simpson, 1980) and is independent of calcium ($Ca^{2+}$) concentration (Simpson, 1989). Internalization is accelerated in an acid medium (Simpson, 1983) and slowed in a cooled system (Simpson, Kamata, and Kozaki, 1990). The Btx molecule must be intact for the light chain to enter the nerve terminus: if the disulphide bind that links the heavy and light chains is broken before the toxin is

internalized into the nerve, the light chain cannot enter and there is no toxicity (Koller et al., 1990).

Intracellular Poisoning: Once the light chain enters the nerve terminus, the disulphide bond between the heavy and light chain is cleaved by an unknown mechanism (Jankovic et al., 1991; Dezfulian and Bartlett, 1984). It is currently believed that the light chain is an enzyme acting as a zinc ($Zn^{2+}$) endopeptidase (Binz et al., 1990; Schiavo et al., 1992) that targets acetylcholine (Ach) release (Dolly et al., 1990). It does not target Ach synthesis or storage as the poisoned nerve can be induced to release normal quanta of Ach through non-physiologic techniques (Dezfulian and Bartlett, 1984; Jankovic et al., 1991). Ach is inhibited when the light chain cleaves one or more proteins of the vesical transport pathway, interfering with proper binding and fusion of the neurotransmitter vesicle to the plasma membrane and impeding exocytotic release of the Ach. Specifically, Btx A cleaves the transport protein known as SNAP-25 which prevents effective docking of the Ach vesicles (Schiavo et al., 1993). Btx blocks exocytosis of neurotransmitter vesicles and interfering with release of quanta of Ach, thereby inhibiting responses evoked by presynaptic stimulation and abolishing endplate potentials (Fletcher et al., 1989; Hunter, 1993).

### A.3.5 Pharmacological Actions: What happens after injection?

The effect of Btx is not immediate: effects begin to emerge 12 hours post-injection and are maximal between 1-2 weeks after injection (Nolan et al, 2000). Post-synaptic action of BTX is indirect, producing "denervation-like" effects on the post-synaptic muscle fibre. Chemical denervation is permanent to the neuromuscular junction: recovery takes place via neurogenesis by the formation of axonal sprouts and new motor endplates (Tsui, 1996). The poisoned motor axon remains in anatomical contact with the muscle endplate, but because neurotransmission is blocked, the muscle fibre is paralyzed (Borodic et al., 1994b). Axonal sprouting takes place within 6-10 days of exposure (Duchen, 1969; Duchen, 1970; Angaut-Petit, 1990). Sprouts appear as thin unmyelinated filaments that run usually parallel to the longitudinal axis of the muscle fibres. Examining muscle-nerve interactions in the orbicularis oculi following treatment for

blepharospasm, Alderson, Holds, and Anderson (1991) found non-collateral sprouting that originated from three sources: 1) the nodes of Ranvier of myelinated parent pre-terminal axons, 2) the unmyelinated terminal axon immediately proximal to the end-plate, and 3) the ultraterminal axon arborization over the endplate. These nerve outgrowths appear as thin filaments, with no more than one per original endplate emerging at this time (Angaut-Petit, 1990). With increased time after poisoning, the axonal sprouts increase in number, length, and complexity, with the general growth direction being parallel to the muscle fibre axis (Angaut-Petit, 1990).

Some muscle fibres in BTX-treated muscle contain more than one endplate, each innervated by separate preterminal motor axons (Alderson et al., 1991). This may occur because functional denervation makes muscle "receptive" to responding to axonal processes to form an endplate region.

Functional recovery of the neuromuscular junctions takes about 3-6 months (Holds et al., 1990). Sprouting and remodeling may continue for up to 3 years post BTX-exposure (Holds et al., 1990). Sprouting occurs at different rates in slow and fast twitch fibres. Nerve sprouts can be seen in the soleus, a predominantly slow-twitch muscle, 4 days after injection and the number of sprouts increases until new endplates are formed by the 6th week (Duchan, 1971). The gastrocnemius, a fast-twitch muscle, reveals axonal sprouting 3-4 weeks after injection and motor end-plate formation approximately 8 weeks post-injection (Duchan, 1971).

There is observed spreading of acetylcholine cholinesterase activity covering most of the toxin-exposed sarcolemma of the muscle (Tsui, 1996). After 4-5 months, the distribution of acetylcholine cholinesterase activity reverts back to the normal pattern of being confined to the motor-endplate regions. Motorneurons exert trophic influences in receptors: in the presence of the appropriate trophic factor, acetylcholine sensitivity and nicotinic acetylcholine receptors (nAChR) are localized to the end-plate region; in the absence of the trophic factor, acetylcholine sensitivity and nAChR's encompass the entire muscle membrane (Simpson, 1977).

In skeletal muscles, two classes of nAChR channels are expressed: a low conductance class of channels (30 pS) present in both embryonic and denervated muscles and 48 pS channels in innervated muscle fibres. The mean open time of the 30 pS embryonic channels is 2-5-fold longer than that of the 48 pS adult ones (Koltgen, 1994). BTX denervation leads to the expression of the embryonic type of the nAChR: a supersensitivity to acetylcholine results (Thesleff, 1960). The nAChR's are co-localised with terminal sprouts; therefore, it is hypothesized that embryonic nAChR channels develop on the muscle fibres and guide the axonal sprouts to form new motor endplates (Valtorta, 1993).

The primary effect of Btx, in addition to paralysis, is muscle atrophy. Muscle atrophy occurs within two weeks of Btx injection in both animal models and muscle biopsy obtained from human patients with blepharospasm (Tsui, 1996). Muscle atrophy continues for 4-6 weeks. Fibre atrophy is indicated by a generalized reduction in fibre diametre and a large degree of fibre variability (Borodic et al., 1994a). The correlation between fibre size (diametre) variability and cholinesterase staining is used to assess therapeutic BTX effects in muscle biopsies (Borodic et al., 1994a). Fibre atrophy is reversible, with recovery after 4-6 months (Borodic et al., 1994a).

ATPase enzyme histochemistry on animal muscle tissues injected with Btx has demonstrated an alteration in the pattern of muscle fibre types; the number of type I fibres increase after injection (Borodic et al., 1994b). Muscle fibres that belong to the same motor unit are morphologically, histochemically, and physiologically similar, with type I fibres being innervated by low-threshold motor neurons and type II fibres being innervated by higher-threshold neurons (Borodic et al., 1994b). In the normal condition, there is a mosaic-like pattern of the distribution of innervation by each motor unit. Although this pattern varies between muscle groups, it can be somewhat compared to a checkerboard. The successful reinnervation of denervated muscle from nearby collateral axon sprouts by a different motor unit type will convert the reinnervated muscle fibre to

that type (Borodic et al., 1994b). As a consequence, the distribution of muscle fibre type changes.

The injected toxin has biological activity at sites distant to the muscle being treated as it diffuses across fascial planes and through bone (Borodic et al., 1990, Borodic et al., 1994b). The size of diffusion field is directly proportional to dose, with the toxin spreading up to 45mm from the injection site in the muscle (Borodic et al., 1994b). Spread to adjacent muscles is common when injecting small muscles, such as those around the eye. For relatively large muscle groups, such as the triceps surae, local diffusion will aid in its effects.

Evidence suggests that Btx may also reach the central nervous system (Habermann, 1974; Gundersen, 1980; Black and Dolly, 1987). After injection of radiolabeled Btx into the gastrocnemius muscles, trace amounts of radioactivity can be detected in the spinal cord segments from which innervation of the injected muscle arises. This is observed in rats within 24 hours after injection (Habermann, 1974) and in cats within 48 hours (Wiegand, Erdmann, and Wellhoener, 1976). The radioactivity (presumed to be toxin) is transported to the spinal cord by retrograde transport through ventral roots.

Btx has been proposed to have central effects in addition to the obvious peripheral effects. Btx is reported to reduce spindle afferent input to the spinal cord by chemically denervating gamma motor neurones to intrafusal fibres (Filippi et al., 1993; Priori et al., 1995; Rosales et al., 1996; Modugno et al., 1998;). In masseter muscles of the rat, Btx injections have been shown to consistently reduce spindle afferent discharges (Filippi et al., 1993), thereby reducing spasticity. Byrnes et al. (1998) hypothesised that by blocking gamma motor neuron transmission, Btx results in reduced spindle activity and that the resulting changes in afferent input lead to a temporary reorganisation of the corticomotor representation towards normal. Gelb et al. (1991) has also suggested that central remodelling takes place after Btx injection. In other words, Btx may induce central remodelling of sensorimotor pathways by altering sensory feedback from the injected region (Ceballos-Baumann et al., 1997; Byrnes et al., 1998; Kanovsky et al., 1998).

*A.3.6   Long term effects*

Very few studies have examined the long-term effects of Btx, partially because the treatment is relatively new and guidelines have not yet been established for its use. A case report on the two-year follow up of a paraplegic patient reveals that the dosage of Btx had to be progressively increased from 100U to 400U to get a similar effect. The decrease in effect over time attributed to a development in Btx antibodies (Al-Khodiary, Gobelet, and Rossier, 1998).

A.3.7   *Preparations*

Btx A is the only serotype commercially available for clinical use. Two preparations exist: Dysport (UK) and BOTOX (USA). There is no differences in the clinical use of the two preparations (Bentivoglio, 1999) but the majority use BOTOX. Although both preparations are measured in mouse units (the amount of the toxin that kills 50% of 18-20g female Swiss-Webster mice), they are not equivalent. Recent studies comparing the potency of the two preparations estimate that one unit of BOTOX is approximately 3-4 times more potent that one unit of Dysport (Krak et al, 1998; Odegren et al., 1998).

*A.3.8   Dose*

The current recommended dose of BOTOX for use in the triceps surae muscle group is 12 U/kg BW (Nolan et al., 2000). This is unsubstantiated and functional improvement has been seen with lower doses (e.g. Cosgrove, Corry, and Graham, 1994; Flett et al., 1999; Sutherland et al., 1999). However, the dosage given has been increasing steadily with increasing experience and lack of side-effects in this pediatric population.

The efficacy of Btx can be enhanced by muscle stimulation and activation during and after injection. The efficacy of Btx is enhanced when the muscle being treated is activated with electrical stimulation during injection (Hesse et al., 1998). Btx injection in the forelimb of adults with writer's cramp is potentiated when 30 min of exercise is performed immediately after injection (Chen et al., 1999).

## A.3.9  Limitations

Two limitations of the use of Btx have emerged: the development of an immune response following successive treatments of large muscles with relatively high doses of toxin (secondary nonresponse) and the existence of patients who are unresponsive to Btx from the first injection (primary nonresponse) (Bentavaglio and Albanese, 1999). In patients with cervical dystonia, about one third of patients do not respond to Btx injections (Jankovic and Schwartz, 1995) and of those, 5-10% are estimated to present antibodies (Borodic et al., 1996). Secondary failure is proposed to be due to changes in the pattern of msucle activity or to undetected neutralising antibodies (Bentavoglio and Albanese, 1999). The efficacy of the drug has been reported to range from 50-60% in children with cerebral palsy (Koman et al, 2000) to 95% in adults with blepharospasm (Dutton, 1996) when injected transcutaneously. The transoral approach was reported to be 100% effective in patients with laryngeal dystonia (Garcia Ruiz et al., 1998). This discrepancy is most likely due to the size and location of the muscles treated as well as the maximum safe dose. Perhaps these limitations can be overcome with the use of different serotypes that have different binding sites and/or higher doses with improved administration.

## A.3.10  History of therapeutic use

The therapeutic use of Btx as a specific, localized muscle relaxant was pioneered in 1973 by an ophthalmologist from San Francisco, Dr. Alan Scott, who published a study on the effect of Btx on the lateral rectus muscle of the monkey (Scott et al., 1973). He was looking for a therapeutic agent that could produce temporary muscle weakness in extraocular muscles as an alternative to surgical treatment of strabismus in children. After testing many substances, Btx A was found to be the best treatment: it induced transient muscle weakness lasting several months without any significant side effects. The first application of Btx in humans was published in 1980 treating patients with strabismus (Scott et al., 1980).

Btx's therapeutic use was extended to blepharospasm (Scott et al., 1985) and hemifacial spasm (Carruthers and Stubbs, 1988) soon after. Once its use was established in the treatment of cervical dystonia (Tsui and Calne, 1987) the most common form of local dystonia, applications in the field of medicine have been extensive (Munchau and Bhatia, 2000).

Because Btx inhibits acetylcholine release at the neuromuscular junction of alpha motoneurons, gamma motoneurons, and parasympathetic and cholinergic postganglionic sympathetic neurons, its use in therapy is being extended. It is commonly used in conditions of muscular overactivity as it induces striated muscle weakness and may alter reflex overactivity by inhibiting transmission of gamma motoneurons in muscle spindles (Priori et al, 1995). Recent clinical evidence is emerging that Btx is effective on autonomic nerve terminals of smooth muscles (Albanese et al., 1995). It is currently being tested as a treatment for overactive smooth muscle (eg achalasia) (Annese et al., 1999; Katzaka and Castell, 1999) and abnormal activity of glands (eg hyperhidrosis) (Naumann et al, 1998; Heckmann et al., 1999).

In 1990, Btx was found to be effective in decreasing muscle spasticity (Snow et al., 1990). Conventional treatments for muscle spasticity including intrathecal baclofen (Penn, 1992), spasmolytic agents, phenol injections (Braun et al., 1973), and various surgical techniques, including tendon transfer, rhizotomy, tenotomy, and osteotomy have not proven satisfactory in a large number of patients (Tsui, 1996), not to mention painful and full of risks. The potential for Btx therapy for conditions characterized by muscle spasticity quickly became apparent.

The first report of the use of Btx in children with cerebral palsy was published in 1993 by Koman et al. Since that date, there has been a push to approve Btx as a treatment for spastic cerebral palsy in children. Btx therapy has recently been approved in Ireland, Australia, and Canada for the treatment of children with cerebral palsy.

*A.3.11 Use in Cerebral Palsy*

Studies examining the effects of Btx injections in children with cerebral palsy have been emerging in the literature. Studies reporting results from Btx injections into the ankle plantarflexors are summarized in Table A-1. Overall, the studies report a reduction in muscle tone and spasticity as measured by the Modified Ashworth Scale in treated muscles and improvements in motion at the affected joint(s) (Koman et al., 1993; Calderon-Gonzalez, 1994; Cosgrove et al., 1994; Corry et al., 1998; Wong, 1998; Flett et al., 1999, Koman et al., 2000). Ambulatory status and gait mechanics have also improved in many children injected with Btx (Koman et al., 1993, 1994; Cosgrove et al., 1994; Corry et al., 1998; Wong et al., 1998; Flett et al., 1999; Sutherland et al., 1999; Koman et al., 2000). Specifically, ankle position and range of motion during both the stance and swing phases of the walking stride are improved after the ankle plantarflexors are treated with Btx (Corry et al., 1998; Sutherand et al., 1999). These changes are still evident 12 weeks post injection (Corry et al., 1998).

Unfortunately, there is a general lack of objective tools to document changes observed in response to Btx injections. The Modified Ashworth Scale was developed to measure degree of spasticity and is commonly used, but it remains subjective and has not been validated in children. The majority of studies noting functional improvements in gait have used a "Physician Rating Scale" (PRS) as opposed to 3-D gait analysis (Koman et al., 1993, 1994; Wong et al., 1998; Flett et al., 1999; Koman et al, 2000). The most commonly used PRS is seen in Table A-2. One comment has been made about the reliability of one PRS used: "...Corry et al. (1998) found good inter-investigator reliability in the assessment of the gait-pattern component" (Koman et al., 2000). However, using Cohen's weighted kappa for agreement of two observers, only footstrike of the affected limb was found to be substantial (weighted kappa of 0.6, 0.6-0.8 denoted as substantial agreement), the rest of the parameters tested (crouch, knee, and change) had no to moderate agreement (Corry et al., 1998). In addition, use of the Gross Motor Function Measure (GMFM) has only been reported in one study (Flett et al., 1999). The GMFM is a readily available tool that has been extensively validated to objectively measure functional improvement motor performance (Russell et al., 1989).

*Table A-1: Summary of published findings of the use of Btx in children with cerebral palsy*

| authors | total n | muscles injected | dose | # injections | results |
|---|---|---|---|---|---|
| Koman et al (1993) | 27 | various | 1-5 U/kg | 1 to 6 | easier positioning, ↓ spasticity, ↑ ROM, ↑PRS |
| Koman et al (1994) | 12 | gastrocs, post tib | 1U/kg | 2 | 5/8 in BTX group and 2/8 in placebo group ↑ PRS |
| Cosgrove et al (1994) | 26 | gastrocs/ soleus, hams | 5-28 U/kg Dysport | 1 | ↓ Ashworth, ↑ ambulatory status in 9/19 |
| Calderon-Gonzalez et al (1994) | 15 | various | 90-300U Dysport | 1 | ↓ Ashworth, no change ROM |
| Densilic and Meh (1995) | 13 | various | 50-500U Dysport total | 2 to 5 | subjective improvement noted in 50-90% |
| Arens et al (1997) | 15 | vatious | 4-6U/kg | 1 | 9/15 improved, 4/15 no change |
| Zelnik et al (1997) | 14 | gastrocs/ soleus | 2-6.8 U/kg | 1 to 2 | ↑ ankle ROM and subjective gait improvement in 9/14 |
| Wong (1998) | 17 | various | 20-50 U total | 1 to 4 | sig. ↓ Ashworth, sig. ↑ ROM, improved ambulatory state in 3, sig ↑ PRS in ambulators |
| Sutherland et al (1999) | 10 | gastrocs | 4U/kg | 2 | sig ↑ df stance and swing, no change passive ankle ROM, normalized EMG in 3/4 |
| Corry et al (1998) | 10 | gastrocs/ soleus | 6-8 U/kg Botox, 15 U/kg Dysport | 1 | sig ↓ Ashworth, sig ↑ passive ankle df, sig ↑ df stance, sig ↑ PRS, no change in passive ankle ROM |
| Flett et al (1999) | 8 | gastrocs/ soleus | 4-8 U/kg | 1 | sig ↓ Ashworth, sig ↑ ankle ROM, sig ↑ GMFM, sig ↑ PRS |
| Koman et al (2000) | 53 | gastrocs | 4U/kg | 1 | sig ↑ PRS, sig ↓ M-wave, no change passive ankle ROM, no change H-reflex |
| Boyd et al (2000) | 25 | gastrocs/ soleus | 5.5-14 U/kg | 1 | sig ↓ Ashworth,sig ↑ ankle df midstance, sig improved ankle moment, no change max ankle df |

sig: reported significance at $p<0.05$
df: dorsiflexion
PRS: Physicians Rating Scale

**Table A-2: Physician Rating Scale (from Koman et al., 1994)**

| Dynamic Function<br>(range of motion) | No. of legs |
|---|---|
| 1. Crouch | |
|     Severe (>20° hip, knee, ankle) | 0 |
|     Moderate (5-20° hip, knee, ankle) | 1 |
|     Mild (<5° hip, knee, ankle) | 2 |
|     None | 3 |
| 2. Equinus Foot | |
|     Constant (fixed contracture) | 0 |
|     Constant (dynamic contracture) | 1 |
|     Occasional heel contact | 2 |
|     Heel-to-toe gait | 3 |
| 3. Hind Foot | |
|     Varus at foot strike | 0 |
|     Valgus at foot strike | 1 |
|     Occasionally neutral at foot strike | 2 |
|     Neutral at foot strike | 3 |
| 4. Knee | |
|     Recurvatum >5° | 0 |
|     Recurvatum 0-5° | 1 |
|     Neutral (no recurvatum) | 2 |
| 5. Speed of gait | |
|     Only slow | 0 |
|     Variable (slow-fast) | 1 |
| 6. Gait | |
|     Toe-toe | 0 |
|     Occasional heel-toe | 1 |
|     Heel-toe | 2 |
| | Total |

### A.3.12 Btx vs serial casting

Only two studies to date have directly compared the effects of serial casting with Btx (Corry et al., 1998; Flett et al., 1999). Both studies have concluded that Btx and serial casting have similar effects, but that Btx has more persistent effects. These two studies report a decrease in spasticity as measured by the Modified Ashworth Scale and improvements in gait as measured by the PRS. Improvements in ankle kinematics measured by 3-D gait analysis were reported by Corry et al. (1998). In addition, Flett et al. (1999) report improvements in motor function as measured by the GMFM. Corry et al. (1998) conclude that that Btx is at least as effective as casting and has more persistent effects in the conservative management of ankle equinus. There are also fewer side effects reported with the Btx group.

In addition, one study has examined the efficacy of Btx with stretching following administration in a group of post-stroke adults (Reiter et al., 1998). A group of hemiparetic patients were injected into the tibialis posterior to treat foot inversion and then their foot was taped for 3 weeks to continuously stretch the muscle. This group was compared to a control group receiving a higher dose of Btx injected into the tibialis posterior, gastrocnemius, soleus, flexor hallicus longus, and flexor digitorum longus. Although both groups exhibited decreases in spasticity as measured by the Modified Ashworth Scale and improvements in ankle dorsiflexion, the group receiving Btx only had a longer decrease in spasticity (measured 3 months after injection). The authors attribute the persistent improvements in ankle dorsiflexion despite a relapse in spasticity in the combined group to increases in muscle length.

Because the dosage of Btx given and the muscles injected were not standardized, it is difficult to draw comparisons as to the beneficial effects of combining Btx with prolonged muscle stretch. It can be argued that because Btx and casting have different modes of action (Btx decreasing the force-generating capacity of the muscle and casting lengthening the musculo-tendinous unit) the two combined should have a more persistent effect than either alone.

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# APPENDIX B: SPASTICITY

## B.1 INTRODUCTION

Spasticty arises from upper motor neuron lesions involving motor cortices and their associated motor pathways. The distribution and severity of the spasticity depends on the site and extent of the brain damage.

The most widely accepted definition of spasticity was put forth by Lance in 1980. Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the upper motoneuron syndrome. This definition emphasizes its reflexive nature and suggests that it is only one component of a more complex disorder.

It is believed that spasticity is related to an increased excitatory state at the segmental spinal level caused by a decrease in inhibition (Delwaide, 1973; Katz and Pierrot-Deseilligny, 1982; Dietz, Quintern, and Berger, 1985). Upper motor neuron lesions damage the pyramidal tract and other motor pathways including the cortico-reticulospinal tract (Mayer, 1997). Increased alpha-motor neuron excitability results acting to increase muscle tone and tendon jerk responses in the affected muscles. Shortening of motoneuron dendrites and collateral sprouting of dorsal root afferents may also play a role (Burke, 1988; Katz and Rymer, 1989). Muscle spindle and microneurographic recordings have ruled out increased muscle spindle sensitivity or increased Ia discharge in response to muscle stretch (Burke, 1983; Burke, 1988; Wilson et al., 1999).

Spasticity is characterised by enhanced stretch reflex activity. The dynamic component of the stretch reflex is clinically manifested as the "catch point" at which a manually

applied stretch is abruptly resisted. With increasing rates of stretch, the catch point occurs at shorter muscle lengths. The static component of the stretch reflex is manifested as continued resistance to muscle stretch. With rapid stretch of a spastic muscle, there is a sudden catch and if the muscle is maintained at that length, the muscle relaxes to allow further lengthening at a slow velocity. Clonus occurs with repeated discharge of this pathway in response to sustained stretch. Accompanying the enhanced stretch reflex is impaired reciprocol inhibition leading to co-contraction of agonist and antagonist muscle groups (Girlanda et al., 1997).

The stretch reflex is evoked by a sudden increase in muscle length resulting in contraction of that muscle. When a muscle is stretched, primary 1a afferents surrounding the intrafusal fibres of the muscle spindle are excited. These 1a afferents enter the dorsal root of the spinal cord and make two synaptic connections. One branch passes directly to the anterior horn of the cord grey matter and excites alpha motor neurons that project back to the muscle of origin as well as to other synergists. The other branch synapses with an inhibitory interneuron which projects to alpha motoneurons of antagonist muscles. When the length of a muscle is suddenly increased, activation of the stretched muscle coincodes with inhibition of the antagonist muscle, a process called reciprocol inhibition.

The stretch reflex, modulated by muscle spindles, can be divided into two components: the static and dynamic stretch reflex. The dynamic component of the stretch reflex is elicited by rapid muscle stretch resulting in a signal being transmitted from primary spindle endings. These signals cause a strong reflex contraction of the muscle from which the signal originated. The function of the dynamic component of the stretch reflex is to oppose sudden length changes of the muscle as it causes muscle contraction that opposes the stretch. After the initial stretch, the weaker static stretch reflex persists as long as the muscle is maintained at an increased length. The static reflex component is evoked by the continuous static receptor signals transmitted from both the primary and secondary spindle endings. The static component continues to cause muscle contraction

as long as the muscle is maintained at an excessive length. The muscle contraction elicited opposes the force that is causing the excess length.

There are also non-reflex or rheologic properties of muscle that contribute to resistance with stretch (Given, Dewald, and Rymer, 1995; Sinkjaer et al., 1988). These rheologic properties involve the plasticity and visco-elasticity of the musculotendinous unit, or Parallel Elastic Component (PEC) according to Hill's muscle model (Hill, 1953). Excessive muscle contraction due to chronic spasticity acts to strengthen and shorten the muscle creating a contracture (Ziv et al, 1984). If a muscle is shortened by a contracture, then a given change in joint angle will stretch the muscle more than normal for that angle, so an increased reflex response may be evoked (Nash, Neilson, and O'Dwyer, 1989). This facilitory influence of muscle length on the stretch reflex has been demonstrated in the gastrocnemius muscle of children with cerebral palsy (Tardieu et al, 1982). Muscle tone or resistance in spastic muscles depends on both the active contractile tension generated by reflex activity and the passive tension generated by the rheologic properties of muscle and other tissues being stretched, with the rheologic contribution (enhanced viscosity) increasing with chronic spasticity (Herman, 1970).

Spasticity impairs postural control, mobility, and function by interfering with voluntary movements. Patients with cerebral lesions usually demonstrate a antigravity postural patterns (Mayer, Esquenazi, and Childers, 1997) with hip adduction, knee extension, and ankle plantarflexion. Shoulder adduction and elbow and wrist flexion occur with upper limb involvement. Spasticity leads to an imbalance of agonist and antagonist muscle groups and chronic shortening of the spastic agonists (Tardieu C et al., 1982; Tardieu G et al., 1982). Without treatment, contractures develop and the ankle remains in an equinus state. Postural control, mobility, and function are hampered. The goal of treatment in patients with spasticity is to reduce the spasticity, thereby maximizing function.

However, there is no reliable or quantitative measurement of spasticity commonly used in clinical practice. As Panizza stated, "...currently physicians usually have very little

difficulty in the diagnosis of spasiticity in most of their patients, but the problem arises when quantitative considerations must be added, probably because spasticity is not a simple entity but a syndrome originating from a variety of disorders" (Panizza, 1995).

The most common form of clinical measurement is the Ashworth Scale (Ashworth, 1964) or the Modified Ashworth Scale (Bohannon and Smith, 1987) which involves manually manipulating the joint and qualitatively assessing the degree of passive resistance based on an ordinal scale (Table B.1-1). Owing to the non-linearity of this measure, results are usually clustered in the middle (Katz and Rymer, 1989) and its reliability has been called into question.

*Table B.1-1: Modified Ashworth Scale for spasticity (Bohannon and Smith, 1987).*

| Grade | Description |
| --- | --- |
| 0 | No increase in muscle tone |
| 1 | Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of range of motion when the affected part(s) is moved in flexion or extension |
| 1+ | Slight increase in muscle tone, manefested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM |
| 2 | More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved |
| 3 | Considerable increase in muscle tone, passive movement difficult |
| 4 | Affected part(s) rigid in flexion or extension |

Bohannon and Smith (1987) examined the reliability of the Modified Ashworth Scale in elbow flexors. They concluded that the scale was too gross to detect incremental changes and questioned the reliability at the ankle joint. "We believe that the reliability we obtained can be attributed, in part, to our experience and extensive manual testing and discussion. Without such collaboration, different results might have been obtained" (Bohannon and Smith, 1987). Sloan et al. (1992) stated that the Modified Ashworth Scale is a satisfactory clinical measure of spasticity in the upper limb but questioned the validity in the lower limb. Allison and Abraham (1995) and Allison, Abraham, and

Peterson (1996) specifically tested the reliability with the ankle plantarflexors, a more complex joint than the elbow. There were mixed results for intrarater reliability and poor results for interrater reliability leading the authors to conclude that "...although marginal reliability has been demonstrated in this study, a larger question which has not been addressed is whether a qualitative ordinal scale is an acceptable measure, regardless of its repeatability". Despite these observations, the Modified Ashworth Scale remains the most common method to assess the degree of spasticity.

The ease and quickness of administration of the Modified Ashworth test is appealing in a pediatric population, especially in children with cerebral palsy, many of whom also have difficulties concentrating and are hyperactive (Berkow, Fletcher, and Beers, 1992). When assessing new treatments, however, the scale is not a sensitive enough measure.

Recent studies are emerging that use more objective measures to assess spasticity in children with cerebral palsy (Otis, Root, and Kroll, 1985; Price et al., 1991; Koman et al., 1994; Alison and Abraham, 1995; Engsberg et al., 1996; Brouwer et al., 1998). However, few studies have objectively assessed the change in spasticity due to treatment (Otis, Root, and Kroll, 1985; Koman et al., 1994; Brouwer et al., 1998). Using a devices controlled by a hand-held crank (Otis, Root, and Kroll, 1985) and springs (Brouwer, 1998), a significant decline in restraint to imposed ankle plantarflexor stretch has been noted after cast removal and this decrease in spasticity has been attributed to an increase in muscle length.

Koman et al., 1994 is the only group to date that has attempted to objectively measure ankle plantarflexor spasticity to determine the impact of Btx on spasticity. Unfortunately, the results were inconsistent and attributed to lack of patient compliance. No attempts have been made since that time to assess the change in spasticity after Btx injections in a reliable, objective, repeatable fashion. The impact that Btx has on the spasticity of the ankle plantarflexors has only been reported from data collected using the subjective Modified Ashworth Scale.

Using a device controlled by a torque motor, we set out to objectively measure spasticity in children with spastic diplegia receiving two different treatments for ankle equinus: Btx and a combination of Btx and serial casting. The purpose of this study was to determine how ankle plantarflexor spasticity is altered by Btx injection and a combination of Btx and serial casting over a 24-week period. It was hypothesized that spasticity would be reduced after both treatments but that there would be a persistent reduction in ankle plantarflexor spasticity in the combined treatment group that lasted for a longer duration than the group receiving Btx alone. A reduction in spasticity would be manifested as a decrease in maximum torque though a given range of motion, an increase in the time to reach peak maximal force, and a decrease in the rate of rise in torque.

## B.2    METHODS

Eight children between the ages of 5-9 years (7.5 ± 1.5 years, mean ± 1SD) at the time of baseline testing were enrolled in this study. The seven male and one female participant were divided into two groups: Botox only (n=5, aged 7.8 ± 1.6 years) and combined Botox with Casting (n=3, aged 6.89 ± 1.4 years).

The study consisted of four testing sessions in addition to treatment over a 6 month period: pre-treatment for baseline, 8 weeks post Btx injection, 18 weeks post Btx injection, and 24 weeks post Btx injection.

Right and then left ankle plantarflexor spasticity was objectively determined using a computer-controlled device specifically designed for this purpose by Jeffrey R. Aitchison in the Mechanical Engineering Department at UBC. Please consult the documentation accompanying the device for specifics (Aitchison, 1996).

The child was seated comfortable in a chair with his/her right leg maximally extended. The leg was braced in this position to minimize knee flexion and/or extension during the testing procedure. The foot was then placed in the footplate and the position of the foot was adjusted such that the lateral malleolus was aligned with the axis of rotation of the

footplate. Nylon straps secured the foot in place and minimize mediolateral movement. The foot was then maximally plantarflexed and the footplate secured at this angle. The angular position of the knee and ankle and the footplate position were recorded for subsequent sessions.

Before conducting the spasticity tests, the anatomic range of motion limits for the right ankle joint before treatment was established and recorded for subsequent sessions. The computer-controlled stepper motor slowly dorsiflexed the foot. The child was asked not to assist or resist the motion of his/her foot and to remain as still and relaxed as possible as the ankle rotated from a plantarflexed to a dorsiflexed position. When maximum ankle dorsiflexion was reached, the stepper motor returned the footplate to its initial position. Maximal dorsiflexion was determined when at least on of the following conditions occurred: the child complained that his/her calf was sore, the torque motor reached its safety cut-out (set at 20 Nm), the clutch "slipped" as resistance was too high, or resistive torque increased in excess of 2Nm per step.

Tests for ankle dorsiflexor spasticity were conducted at speeds of 60, 70, 80, 90, and 100°/s through the entire range of ankle joint motion previously determined. The foot was moved through the pre-determined range at 60°/s and then held at that position for approximately 4 seconds. The footplate then was slowly returned to its starting position in preparation for the next test, at 70°/s. This continued until all five speeds were tested, for 60 to 100°/s. This procedure was then repeated for the left limb.

At each follow-up session, the child was positioned with the knee and ankle in the same degree of extension as was at baseline testing. The foot-plate of the device was in the same position as before and the ankle was moved through the identical range of motion.

Resistive torque of the ankle plantarflexors and angular position of the ankle joint were recorded at 25Hz by a computer-controlled 12-bit A/D board for each test. Resistive torque of the ankle plantarflexors and angular position of the ankle were recorded. From these data, maximum torque, time to maximum torque, and rate of rise of torque were

determined (Figure B.2-1) and analysed using a 2(group) x 2(foot) x 4(day-pre, wk8, wk18, wk24) repeated measures ANOVA with repeated measures on the day factor. The level of significance was set a priori at $\alpha=0.05$.
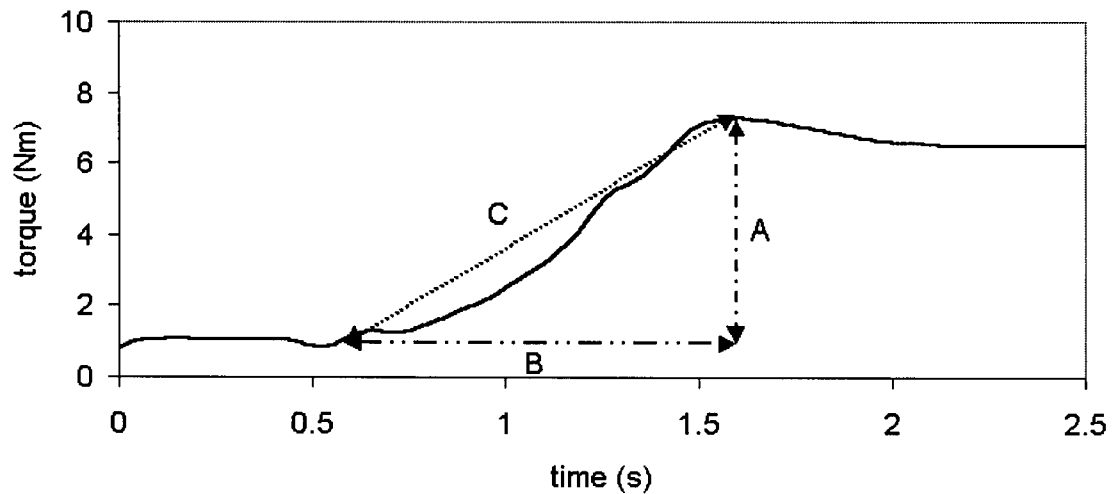


*Figure B.2-1: Sample torque recording from one subject at 60%s. The variables analysed were (A) maximum resistive torque, (B) time to maximum torque, and (C) rate of rise of torque.*

## B.3   RESULTS

One subject in the Btx only group did not attend the 24-week testing session due to illness. In addition, results were not obtained for two of the subjects in the combined treatment group at 24-weeks post-injection due to mechanical difficulties with the equipment.

A sample chart depicting the torque output of one subject at two different speeds of ankle dorsiflexion is seen in Figure B.3-1.

### B.3.1   Maximum Resistive Torque

There was a significant time effect at all velocities of stretch, with maximum torque increasing through 18 weeks post Btx injection (Table B.3.1-1). Maximum resistive torque was decreased by 24-weeks post injection. There were no group effects.
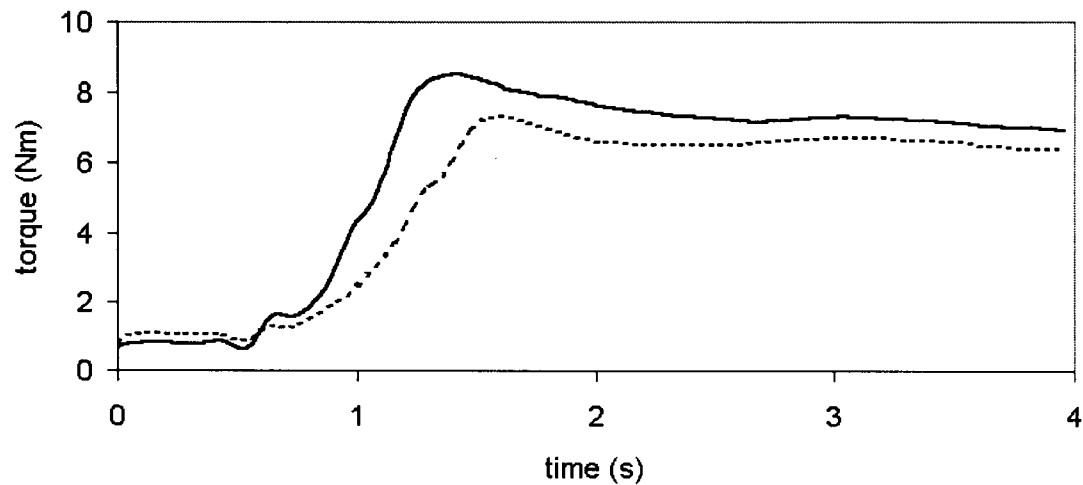
*Figure B.3.1-1: Example of resistive torque measured at a subject's left ankle at 60 (dashed line) and 100 %s (solid line) eight weeks post Btx injection.*

*TableB.3.1-1: Mean maximum resistive torque (±SD) of the ankle plantarflexors of each group across 24-weeks.*

| | Pre | Wk8 | Wk18 | Wk24 |
|---|---|---|---|---|
| **60°/s *** | | | | |
| Btx | 6.6±1.8 | 9.6±4.0 | 10.5±2.5 | 8.26±1.6 |
| Btx + Cast | 13.5±2.0 | 13.5±4.5 | 14.5±5.0 | 20.1[a] |
| **70°/s *** | | | | |
| Btx | 7.4±1.7 | 10.9±4.3 | 10.0±1.8 | 9.7±0.2 |
| Btx + Cast | 12.3±2.5 | 13.9±4.7 | 14.2±3.9 | 15.7 [a] |
| **80°/s *** | | | | |
| Btx | 6.9±1.4 | 10.1±4.1 | 9.7±1.9 | 7.8±1.2 |
| Btx + Cast | 11.3±1.9 | 13.0±3.1 | 14.6±4.9 | 12.7 [a] |
| **90°/s *[Φ]** | | | | |
| Btx | 7.0±1.6 | 9.8±4.8 | 9.7±3.6 | 7.4±0.7 |
| Btx + Cast | 10.7±1.6 | 13.0±2.5 | 13.7±3.4 | 15.3 [a] |
| **100°/s *[Φ]** | | | | |
| Btx | 6.9±2.4 | 8.9±4.3 | 9.7±2.2 | 8.8±3.3 |
| Btx + Cast | 9.9±2.2 | 11.8±2.4 | 13.0±3.7 | 7.7 [a] |

* significant time effect ($p<0.05$)

[Φ] significant group by time interaction ($p<0.05$)

[a] no SD given as only one subject completed this test

*B.3.2  Time to Maximum Resistive Torque*

A time effect was observed at all velocities of stretch with time to maximum torque being increased to 18 weeks after injection and declined at 24 weeks post injection (Table B.3.2-1). There was also a group effect noted at 70, 80, and 90°/s with time to maximum torque being greater in the combined group.

*Table B.3.2-1: Mean time to maximum resistive torque (±SD) of the ankle plantarflexors across the 24-week testing period.*

| | Pre | Wk8 | Wk18 | Wk24 |
|---|---|---|---|---|
| **60°/s *** | | | | |
| Btx | 0.77±0.2 | 0.80±0.3 | 0.98±0.3 | 1.1±1.0 |
| Btx + Cast | 0.81±0.1 | 1.1±0.3 | 1.07±0.2 | 0.80 [a] |
| **70°/s *$^{\Delta}$** | | | | |
| Btx | 0.75±0.2 | 0.83±0.2 | 0.77±0.2 | 0.56±0.1 |
| Btx + Cast | 0.81±0.1 | 0.97±0.3 | 0.98±0.2 | 0.60 [a] |
| **80°/s *$^{\Delta}$** | | | | |
| Btx | 0.69±0.2 | 0.98±0.6 | 0.82±0.1 | 0.81±0.4 |
| Btx + Cast | 0.66±0.1 | 0.93±0.3 | 0.97±0.1 | 0.56 [a] |
| **90°/s *$^{\Delta}$** | | | | |
| Btx | 0.72±0.2 | 0.76±0.1 | 0.68±0.2 | 0.57±0.1 |
| Btx + Cast | 0.57±0.1 | 0.85±0.2 | 0.84±0.2 | 0.84 [a] |
| **100°/s *** | | | | |
| Btx | 0.60±0.1 | 0.70±0.2 | 0.73±0.1 | 0.59±0.1 |
| Btx + Cast | 0.52±0.1 | 0.75±0.2 | 1.07±0.3 | 0.76 [a] |

\* significant time effect ($p<0.05$)

$^{\Delta}$ significant group effect ($p<0.05$)

[a] no SD given as one subject completed this test

*B.3.3  Rate of Rise of Torque*

There was a group effect at all stretch velocities, with the combined treatment group having a greater rate of rise of torque than the group receiving Btx only (Table B.3.3-1).

*Table B.3.3-1: Mean rate of rise of torque (±SD) of the ankle plantarflexors of both groups across the 24-week testing period.*

| | Pre | Wk8 | Wk18 | Wk24 |
|---|---|---|---|---|
| **60°/s** [Δ] | | | | |
| **Btx** | 7.9±3.8 | 11.1±3.2 | 10.0±2.0 | 10.3±6.3 |
| **Btx + Cast** | 15.6±2.2 | 12.3±4.9 | 13.8±8.0 | 24.1 [a] |
| **70°/s** [Δ] | | | | |
| **Btx** | 9.7±5.4 | 12.6±4.4 | 12.8±5.1 | 16.0±3.5 |
| **Btx + Cast** | 14.3±3.0 | 14.8±6.9 | 14.5±6.7 | 24.7 [a] |
| **80°/s** [Δ] | | | | |
| **Btx** | 9.1±2.3 | 11.6±6.0 | 10.9±1.7 | 10.8±6.4 |
| **Btx + Cast** | 15.9±3.3 | 14.5±5.5 | 14.4±5.0 | 21.4 [a] |
| **90°/s** [Δ] | | | | |
| **Btx** | 9.4±3.9 | 10.0±7.0 | 13.0±3.5 | 12.0±3.0 |
| **Btx + Cast** | 18.3±6.0 | 15.1±4.8 | 16.2±6.4 | 17.2 [a] |
| **100°/s** [Δ] | | | | |
| **Btx** | 10.5±3.9 | 11.9±5.0 | 12.2±2.1 | 15.6±11.6 |
| **Btx + Cast** | 17.6±2.5 | 15.6±4.9 | 12.1±4.4 | 9.0 [a] |

[Δ] significant group effect ($p < 0.05$)

[a] no SD given as only one subject completed this test

## B.4 DISCUSSION

It has been reported that both serial casting and Btx can be used to decrease spasticity of the ankle plantarflexors (Otis, Root, and Kroll, 1985; Brouwer et al., 1998; Flett et al., 1999; Koman et al., 2000; Tardieu C et al., 1982; Tardieu G et al., 1982). It was therefore hypothesized that spasticity of this muscle group (as measured by resistive torque and its components) would be decreased after both treatments and would gradually return to pre treatment levels, the patients receiving both Btx and casting having a more persistent decrease in spasticity than the other group.

Unfortunately, there were inconsistent results found with all variables tested. The time effect observed in maximum resistive torque suggests that spasticity increased after treatment until 18 weeks and then decreased by 24 week post Btx injection. However, the time effect of time to maximum torque reveals the opposite, that spasticity decreased to week 18 and then increased at 24 weeks post Btx injection. Similarly, there was a group effect observed with time to maximum torque indicating that the combined group's

ankle plantarflexors were less spastic that the Btx only group. In direct conflict with this finding, the group effect observed with rate of rise of torque indicates that the combined group had more spastic ankle plantarflexors. Because of these conflicting results, no conclusions can be drawn at this time, only suggestions as to why these results were observed.

The reliability of this device has not been thouroughly tested in this population and is considered to be the most prominent issue with the use of this device. In pilot testing of adults and children without spasticity and in a child with spasticity, this device appeared to be reliable. Consistent, believable results were obtained. However, the children evaluated in this study had difficulty complying with this portion of the test, even though it required the least amount of effort and concentration of the test battery. Perhaps this population of children is unable to attend to the task at hand as it is relatively lengthy (approximately 10 minutes per leg) and requires the child to relax and remain relatively motionless. Children with cerebral palsy are known to be hyperactive and have a short attention span (Berkow, Fletcher, and Beers, 1992). Koman et al. (1994) has also made an attempt to objectively measure ankle plantarflexor spasticity after treatment with Btx and reported inconsistent results. The inconsistent results were attributed to subject non-compliance.

Muscle activity of the lower limb was not recorded with this protocol so we were unable to determine if the child was assisting or acting against the movement of the foot-plate during testing. Observing the muscle activity in various muscles of the lower limb during testing would enable the practitioner to gauge when to begin a test (when the child is not activating muscles) as well as what tests are successful (no voluntary activation during movement).

For each testing session, the child was positioned with the same degree of knee and ankle flexion and extension but the position of other parts of the body were not standardised. Although the leg remained relatively stationary throughout testing and the subjectes were asked to remain as stationery as possible, there was still movement of the upper and

lower body throughout testing. Bracing the knee kept it in the same degree of extension in the sagittal plane but did not stop lateral movments during testing or between trials. Brouwer et al. (1998) have a similar device to the one that was used in this study the exception being that it is spring driven. Their device has telescoping rests for the thigh and shank segment that prevent movement in all directions. This addition to our device would be useful for future studies.

A range of speeds of ankle dorsiflexion were used in this study as there is no agreed upon speed of ankle dorsiflexion to test spasticity reported in the literature. When using the Modified Ashworth Scale to determine spasticity, the ankle is simple dorsiflexed relatively quickly and resistance to motion noted. We chose to use a range of speeds (from 60°/s to 100°/s) as it seemed similar to those speeds used by the orthopaedic surgeon involved when using the Modified Ashworth Scale of spasticity. However, the range of speeds used in this study allow for children to react to the movement as it is taking place. Brouwer et al. (1998) used only one speed of movement as their device is spring driven at a range of 350-400°/s which seems more practical to use with this population. We were unable to match this speed due to limitations with the equipment. Upon retrospect, faster speeds would be more advantageous in this group of children as it gives them no time to react to the imposed movement.

Although the results obtained in this study are inconsistent and no conclusions can be drawn as to how spasticity of the ankle plantarflexors is affected by either Btx or a combination of both Btx and serial casting, the objective measurement of spasticity is a required in this area of research. The device used in this study is one method that can be used to measure spasticity of the ankle plantarflexors in an objective, repeatable fashion. The continued development of this device and others like it is a positive step to objectively determine spasticity and the effects that different treatments have on muscle tone.
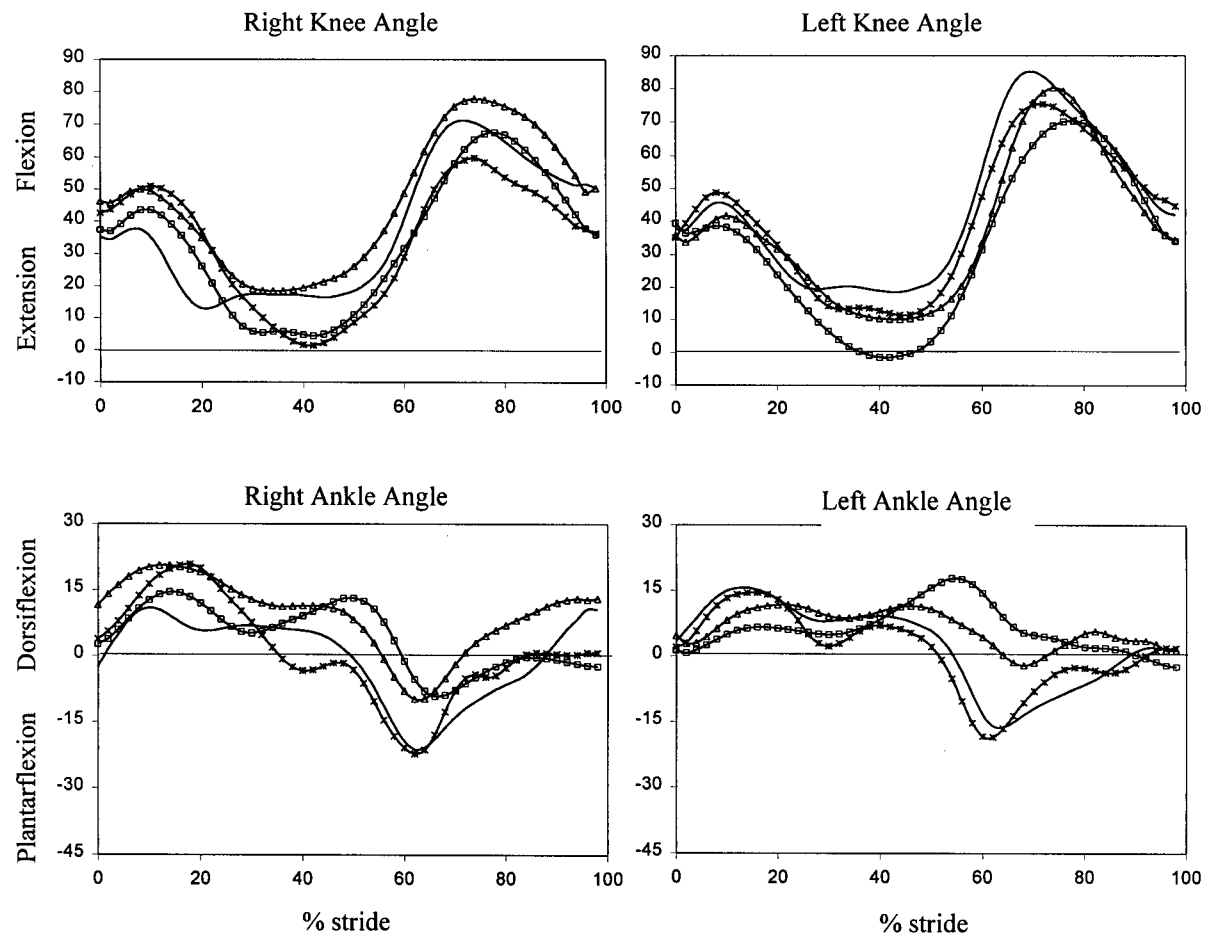
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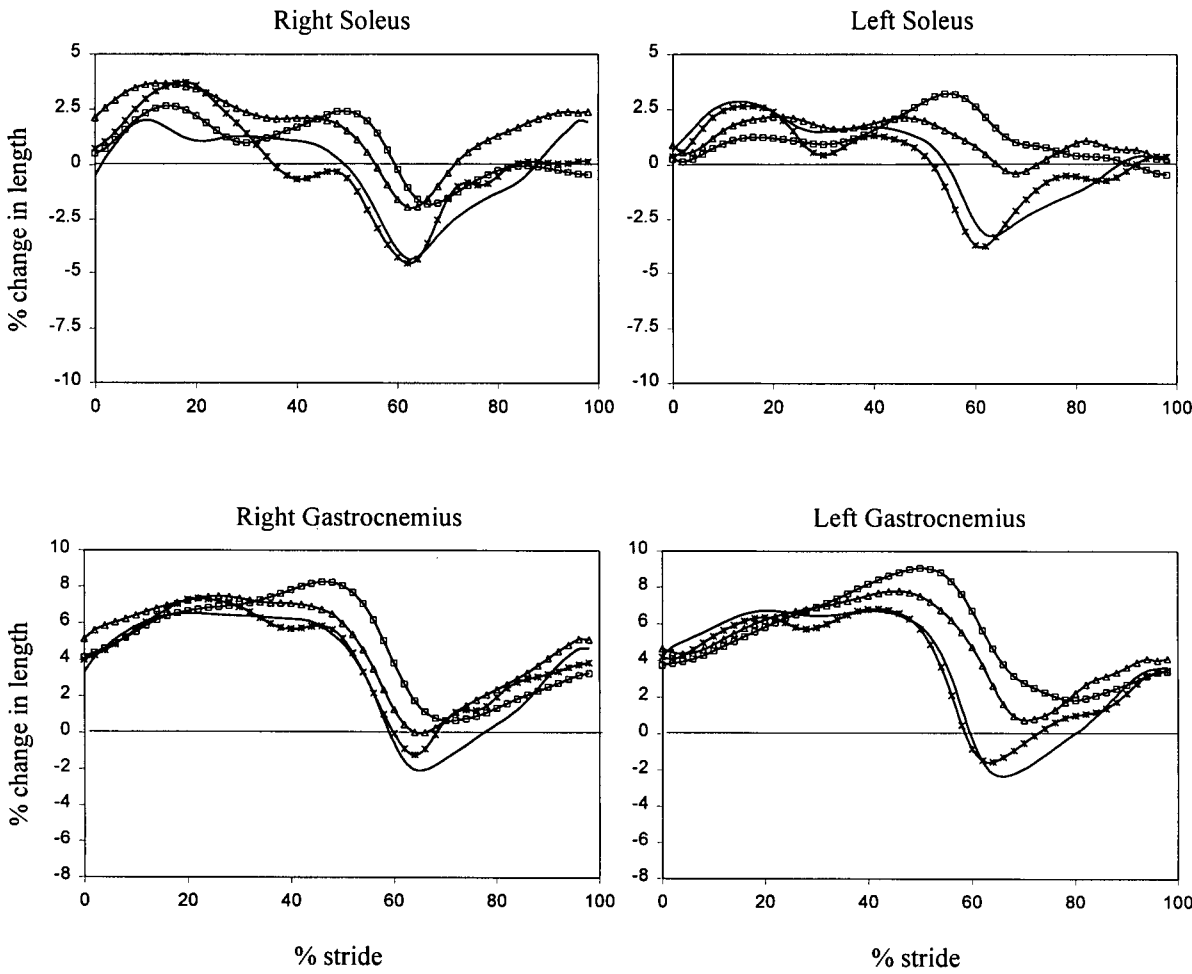
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# APPENDIX C: SUBJECT DATA

## C.1 SUBJECT 1: BTX + CASTING

*Gait Kinematics*



Right Knee Angle

Left Knee Angle

Right Ankle Angle

Left Ankle Angle

% stride

% stride

Pre ——△—— wk8 ——□—— wk18 ——✳—— wk24

*Muscle Lengths*



Right Soleus

Left Soleus

Right Gastrocnemius

Left Gastrocnemius

% change in length

% stride

Pre    wk8    wk18    wk24

*Gait Kinetics*



Right Vertical GRF

Left Vertical GRF

Right Ankle Moment

Left Ankle Moment

Right Ankle Power

Left Ankle Power

% stride
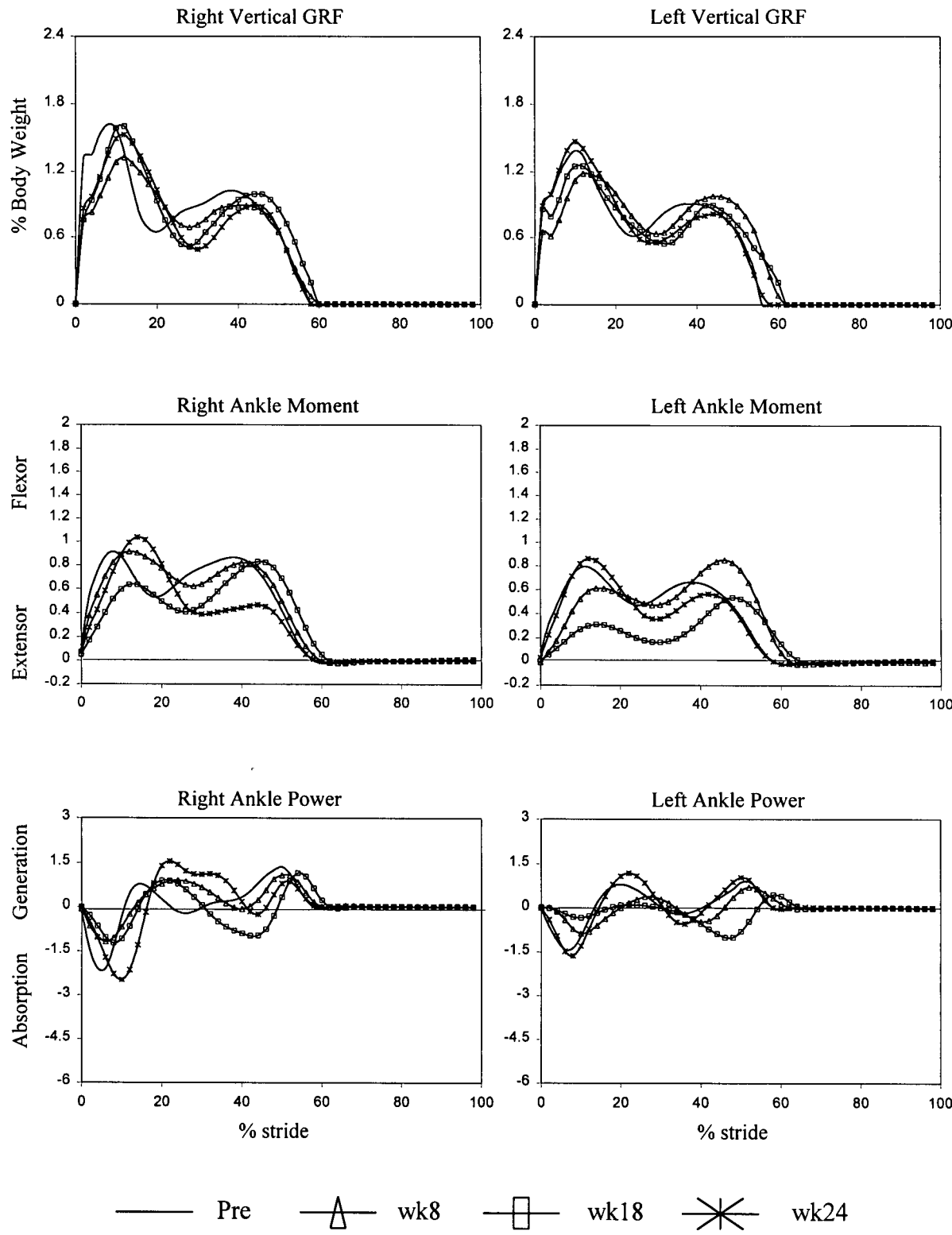
Pre ——— wk8 —△— wk18 —□— wk24 —✳—

## C.2    SUBJECT 2: BTX

*Gait Kinematics*



Right Knee Angle

Left Knee Angle

Right Ankle Angle

Left Ankle Angle

Pre   wk8   wk18   wk24

*Muscle Lengths*



Right Soleus

Left Soleus

Right Gastrocnemius

Left Gastrocnemius

% change in length

% stride

Pre ——— wk8 —△— wk18 —☐— wk24 —✳—

*Gait Kinetics*



Right Vertical GRF

Left Vertical GRF

Right Ankle Moment

Left Ankle Moment

Right Ankle Power

Left Ankle Power
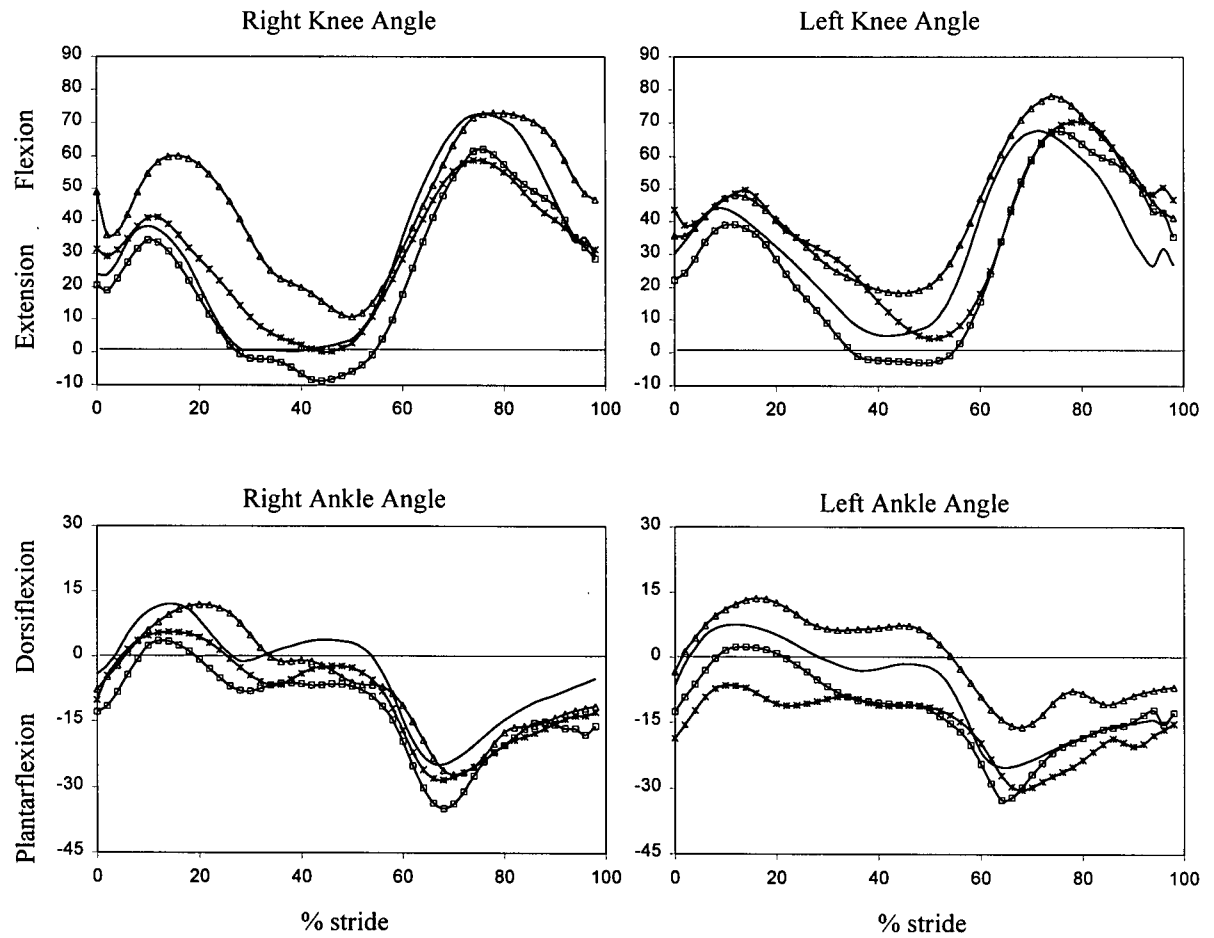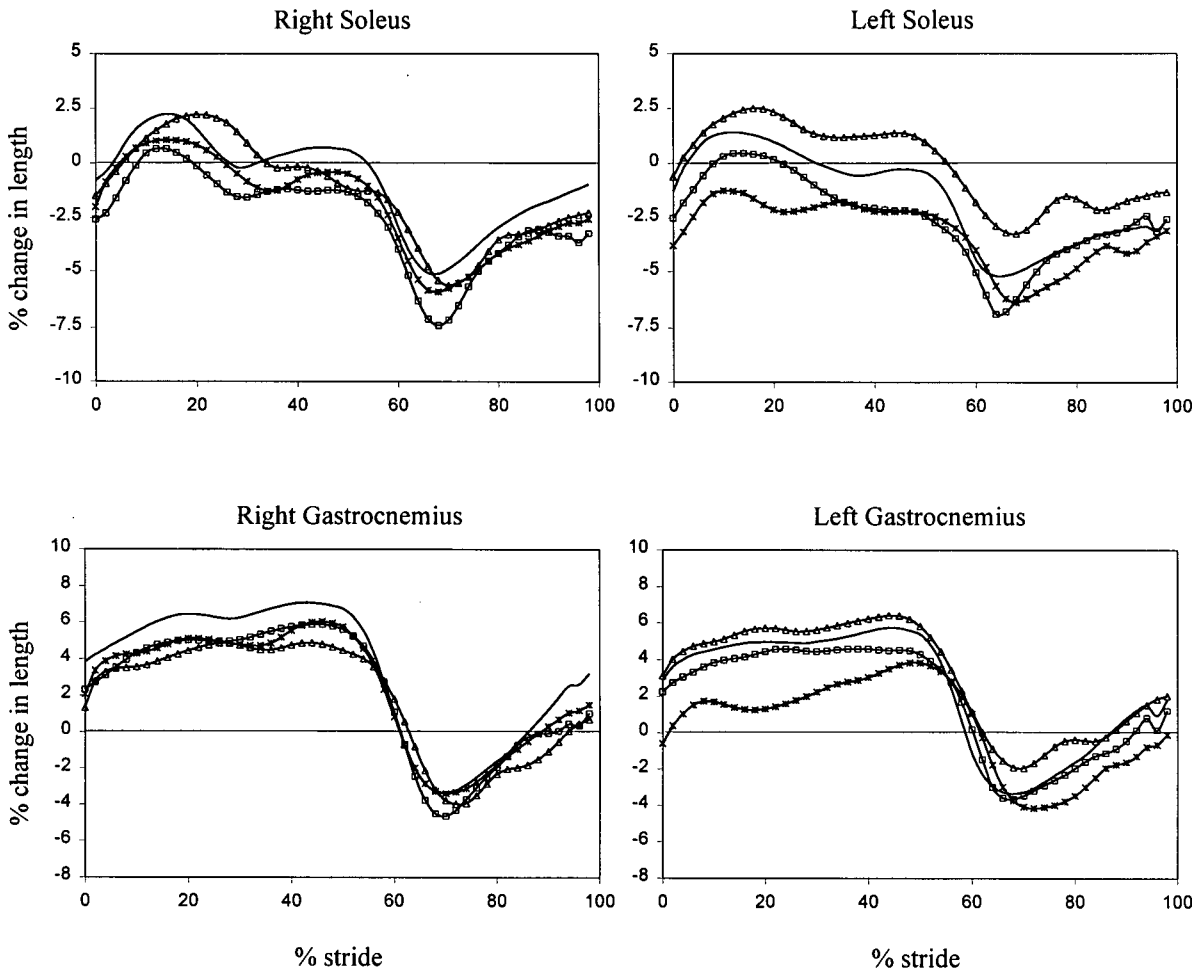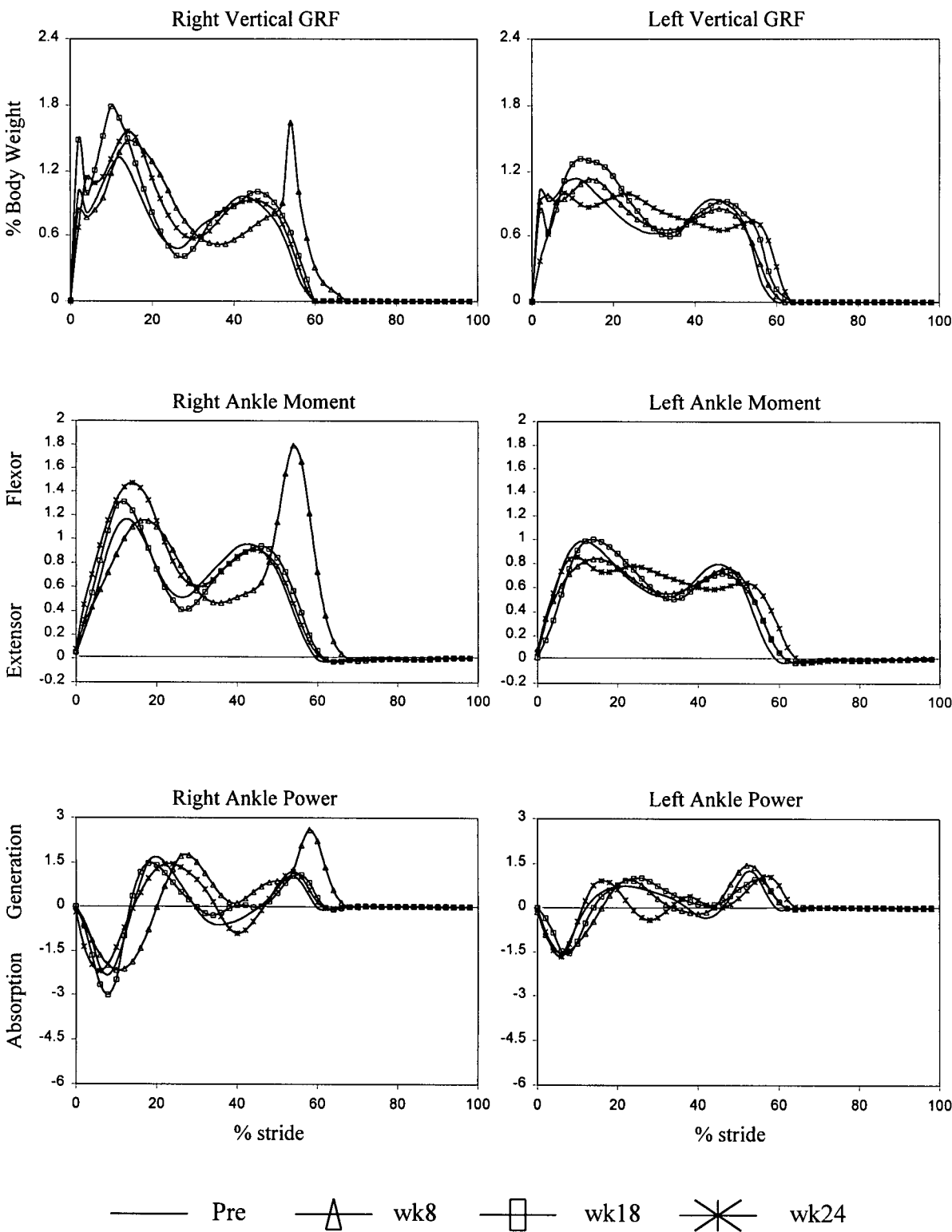
Pre — wk8 — wk18 — wk24

## C.3   SUBJECT 3: BTX + CASTING

*Gait Kinematics*



Right Knee Angle     Left Knee Angle
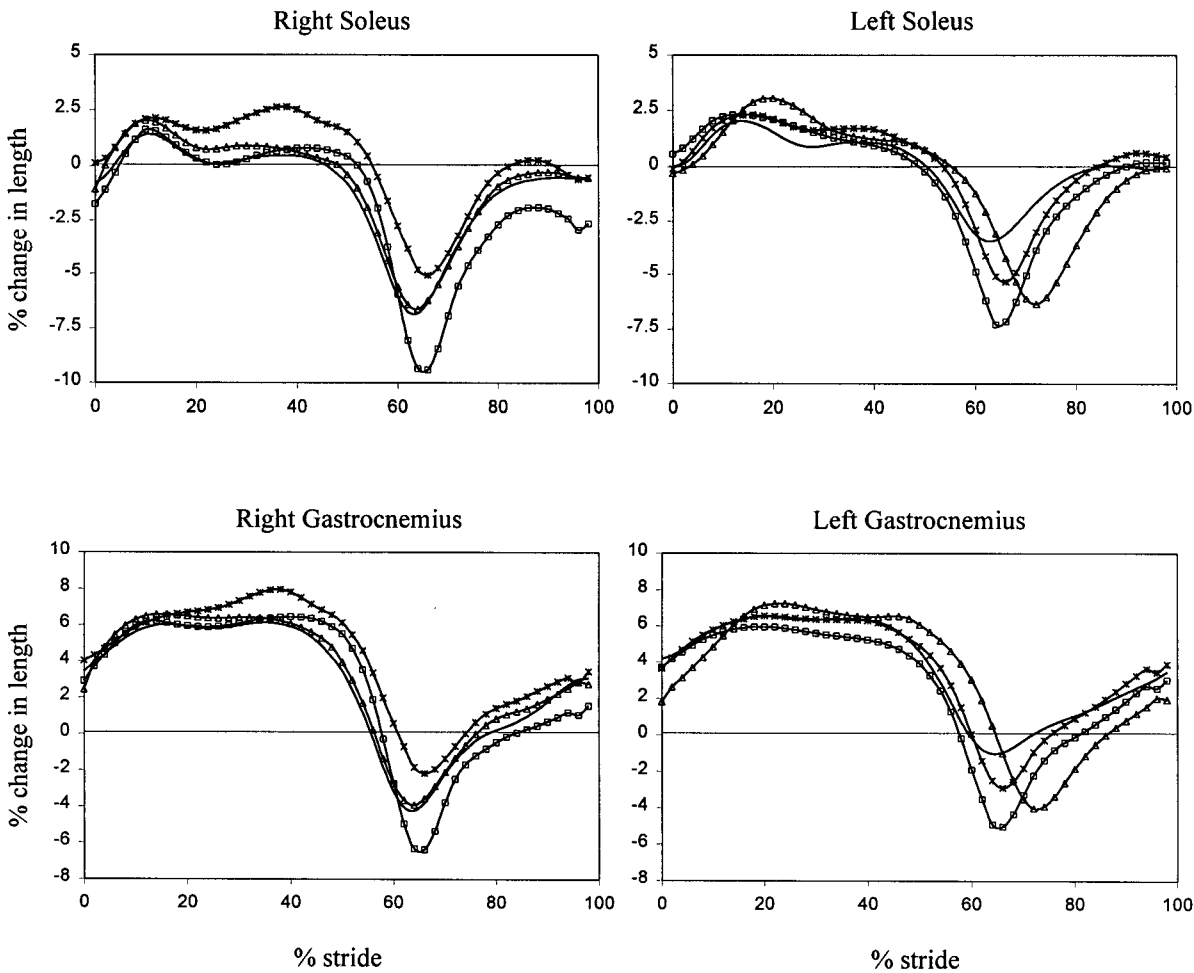
Right Ankle Angle     Left Ankle Angle

% stride     % stride

——— Pre    —△— wk8    —☐— wk18    —✳— wk24

*Muscle Lengths*

### Right Soleus



### Left Soleus



### Right Gastrocnemius



% stride

### Left Gastrocnemius



% stride

Pre ——— wk8 —△— wk18 —□— wk24 —✳—

*Gait Kinetics*



Right Vertical GRF

Left Vertical GRF

Right Ankle Moment

Left Ankle Moment

Right Ankle Power

Left Ankle Power

% stride
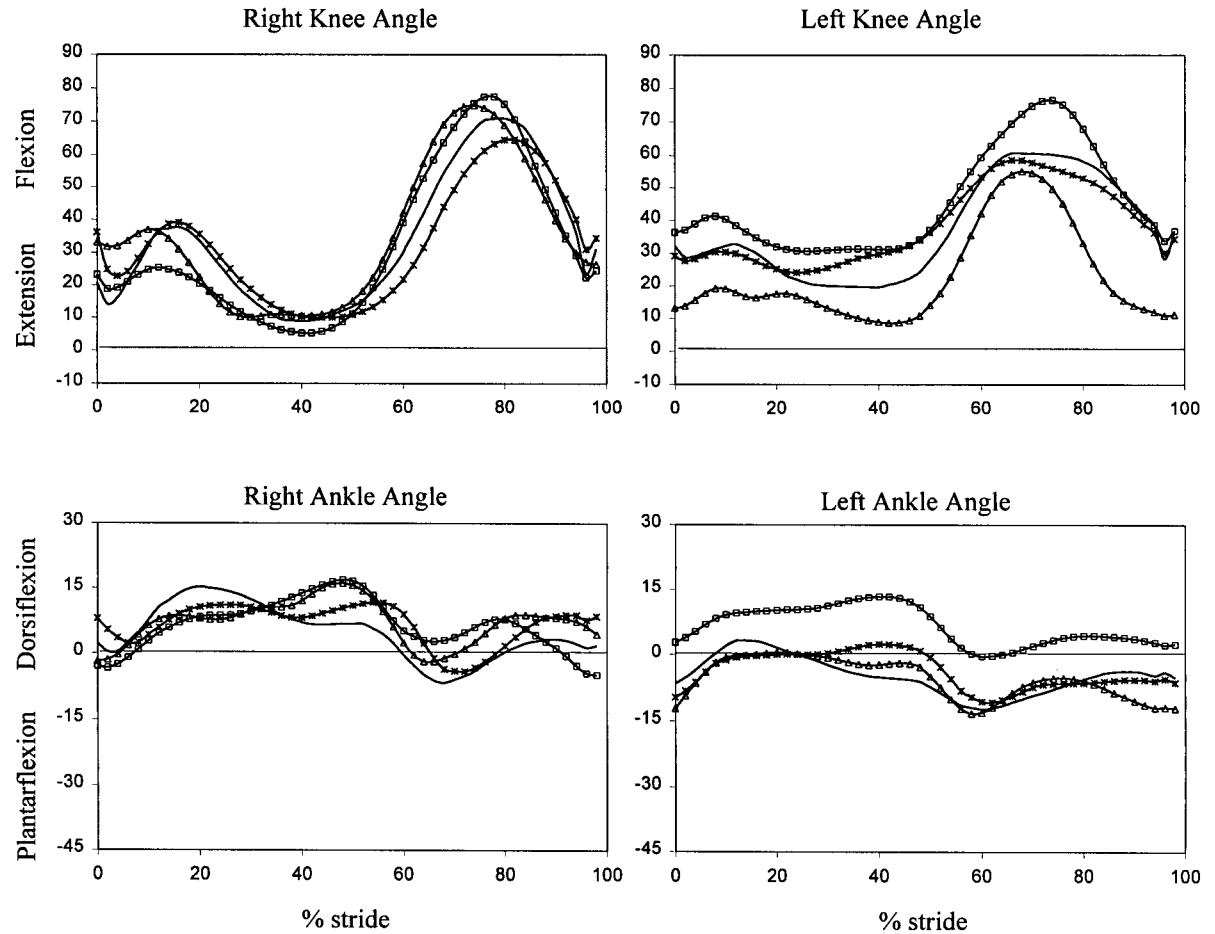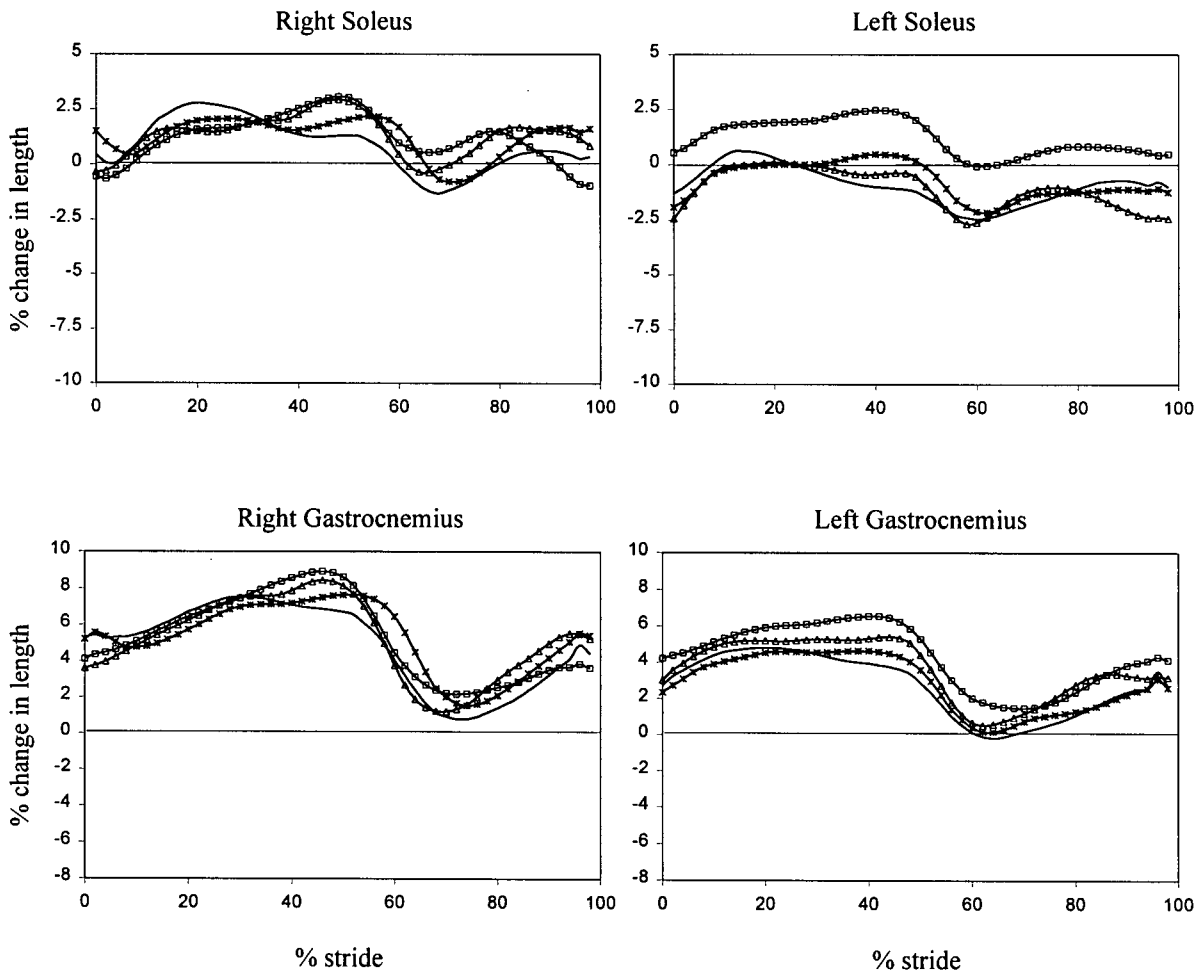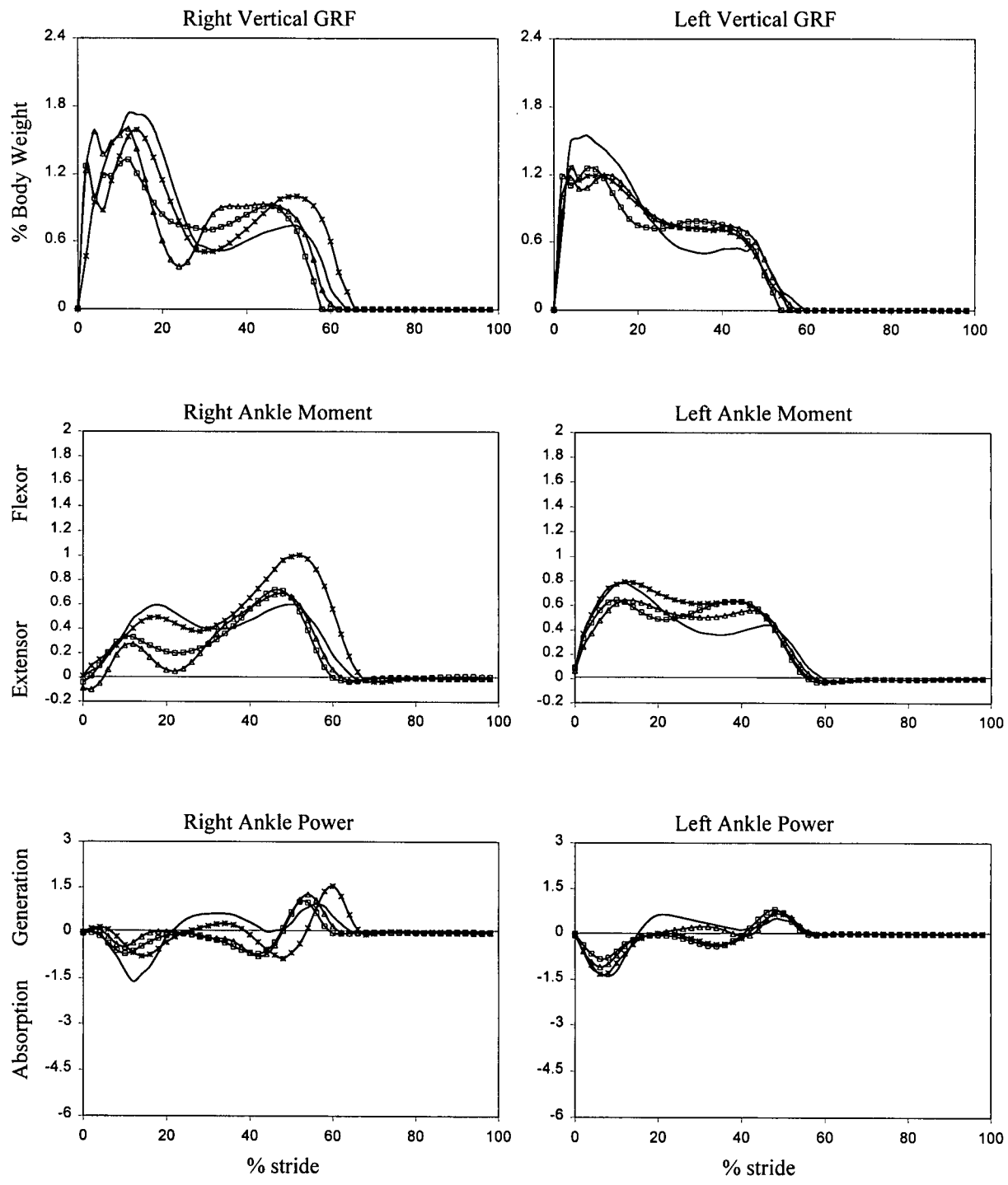
——— Pre ——△—— wk8 ——□—— wk18 ——※—— wk24

## C.4    SUBJECT 4: BTX

*Gait Kinematics*

Right Knee Angle

Left Knee Angle

Right Ankle Angle

Left Ankle Angle

% stride

% stride

Pre ——— wk8 —△— wk18 —□— wk24 —✳—

*Muscle Lengths*



Right Soleus

Left Soleus

Right Gastrocnemius

Left Gastrocnemius

% stride

% stride

Pre —△— wk8 —□— wk18 —✳— wk24

*Gait Kinetics*



Right Vertical GRF — Left Vertical GRF — Right Ankle Moment — Left Ankle Moment — Right Ankle Power — Left Ankle Power
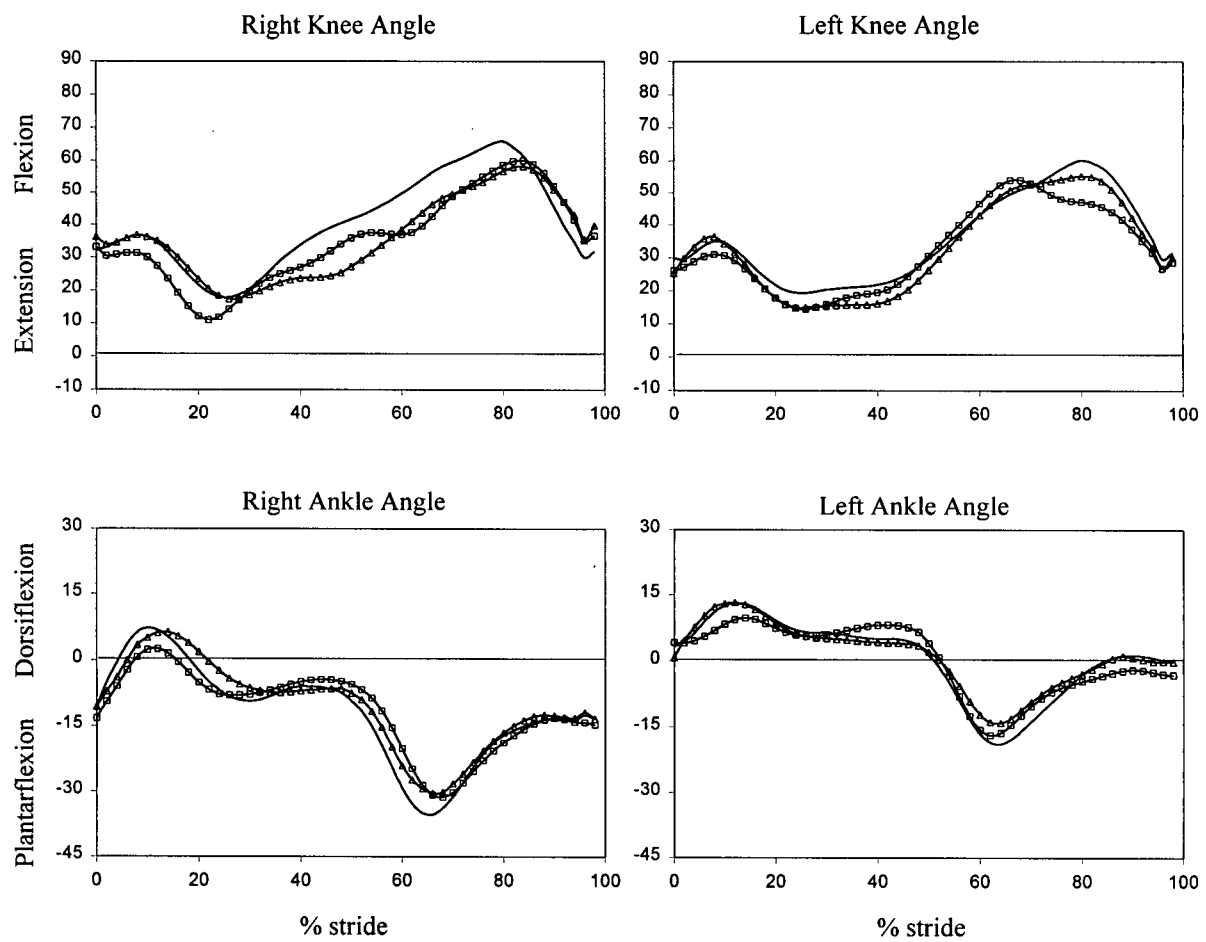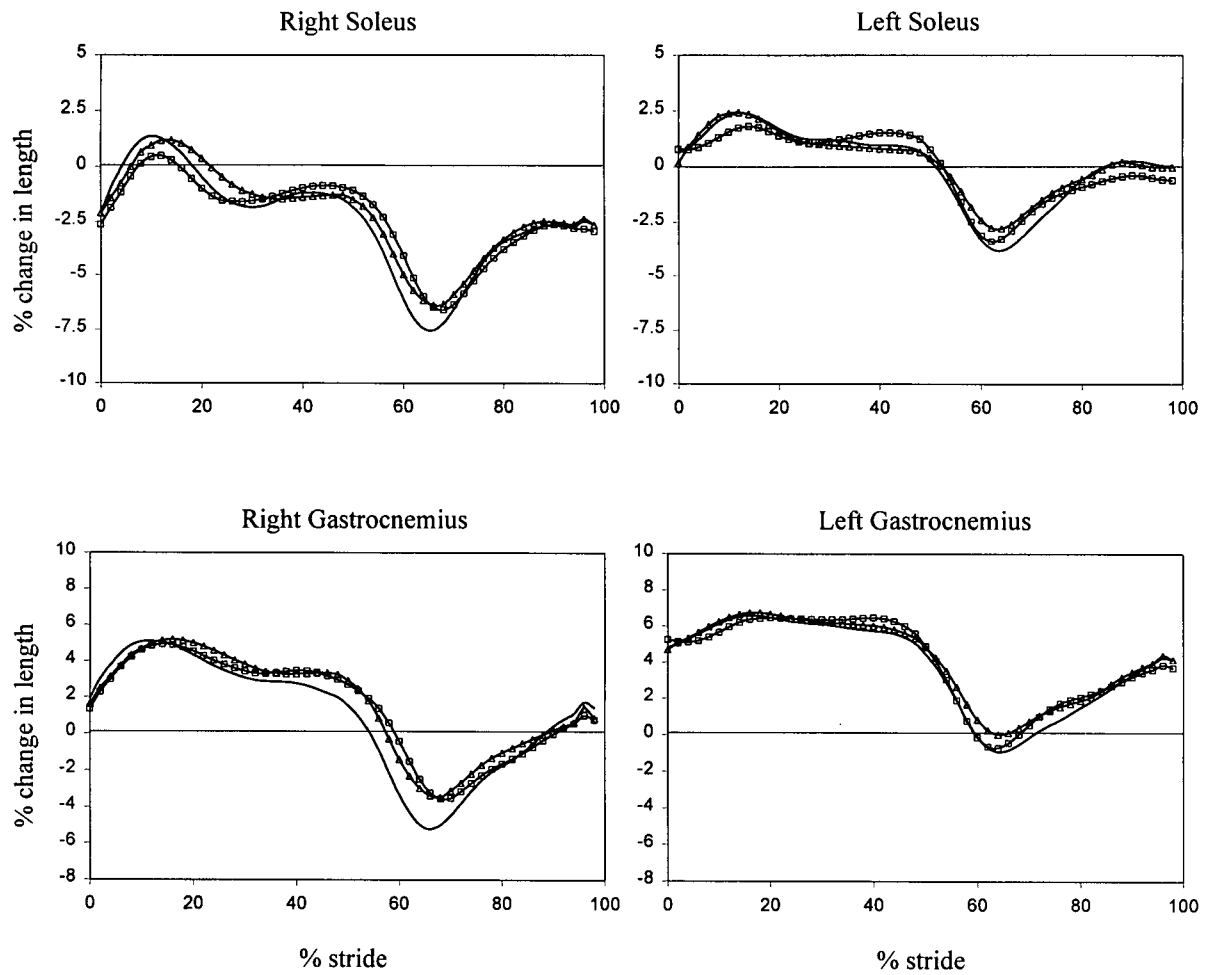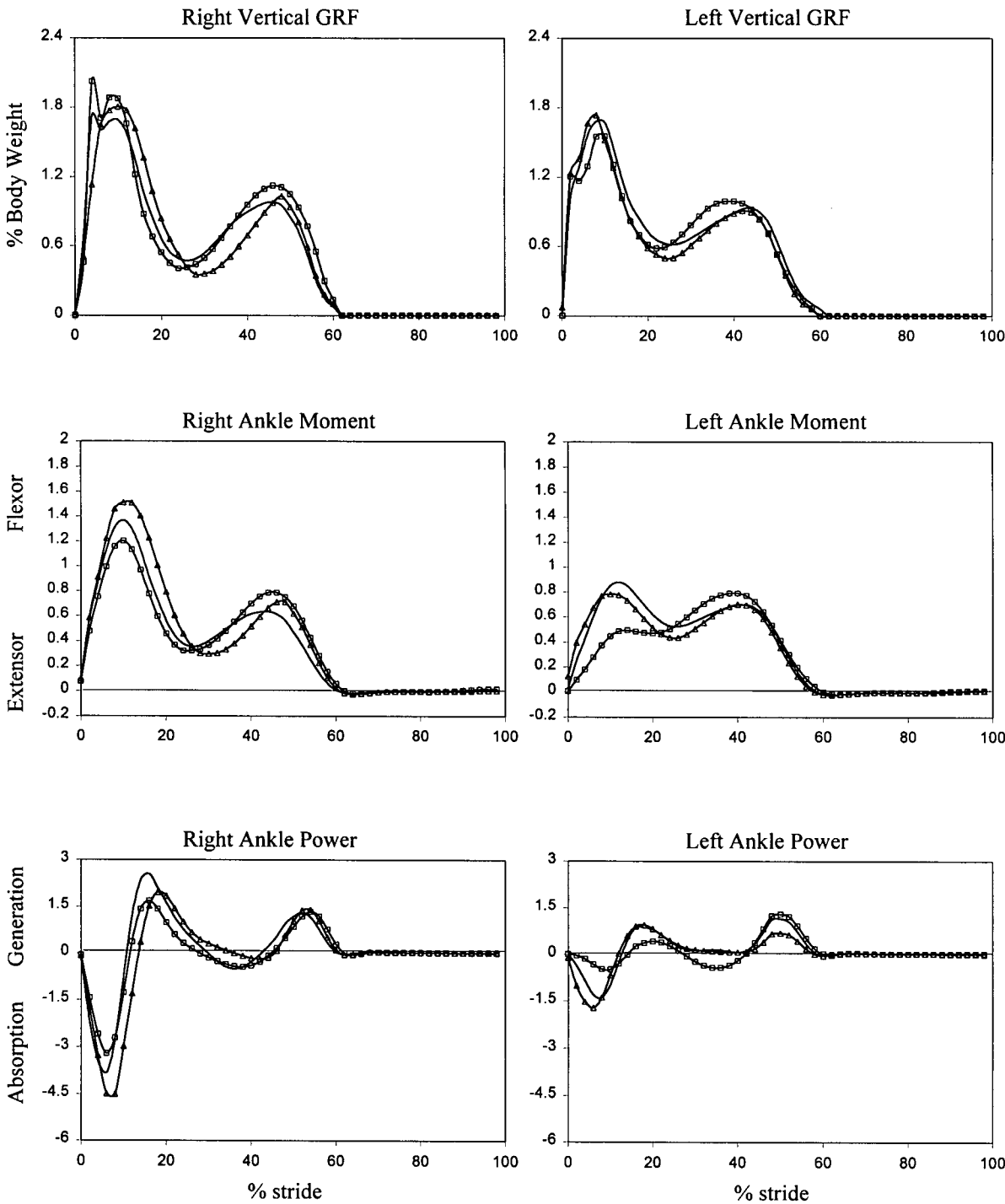
Pre      wk8      wk18      wk24

## C.5 SUBJECT 5: BTX

*Gait Kinematics*



Right Knee Angle

Left Knee Angle

Right Ankle Angle

Left Ankle Angle

% stride

% stride

―――― Pre    ―△― wk8    ―□― wk18    ―※― wk24

*Muscle Lengths*



Right Soleus      Left Soleus

Right Gastrocnemius      Left Gastrocnemius

% change in length

% stride      % stride

——— Pre    —△— wk8    —□— wk18    —✳— wk24

*Gait Kinetics*



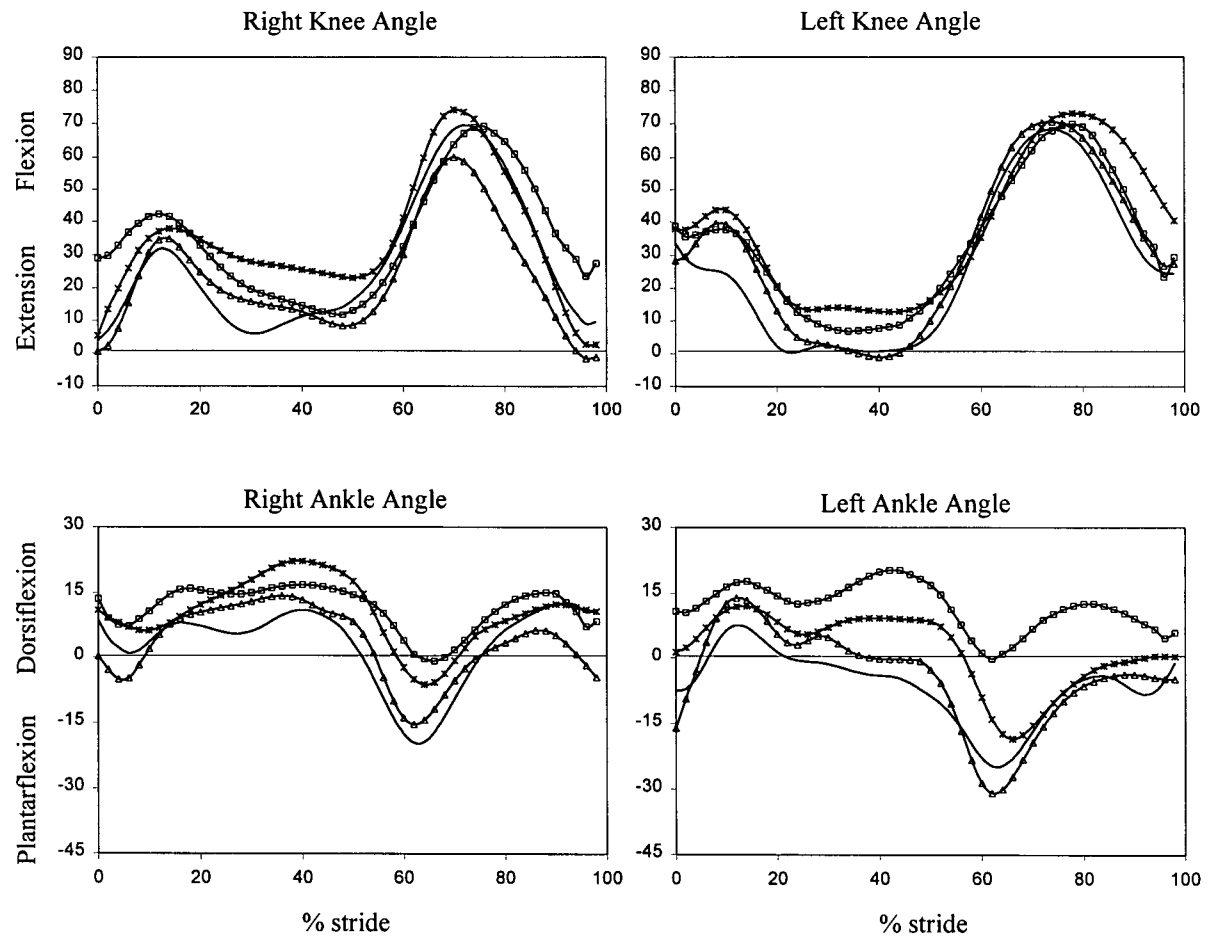Right Vertical GRF     Left Vertical GRF

Right Ankle Moment     Left Ankle Moment

Right Ankle Power     Left Ankle Power

% stride
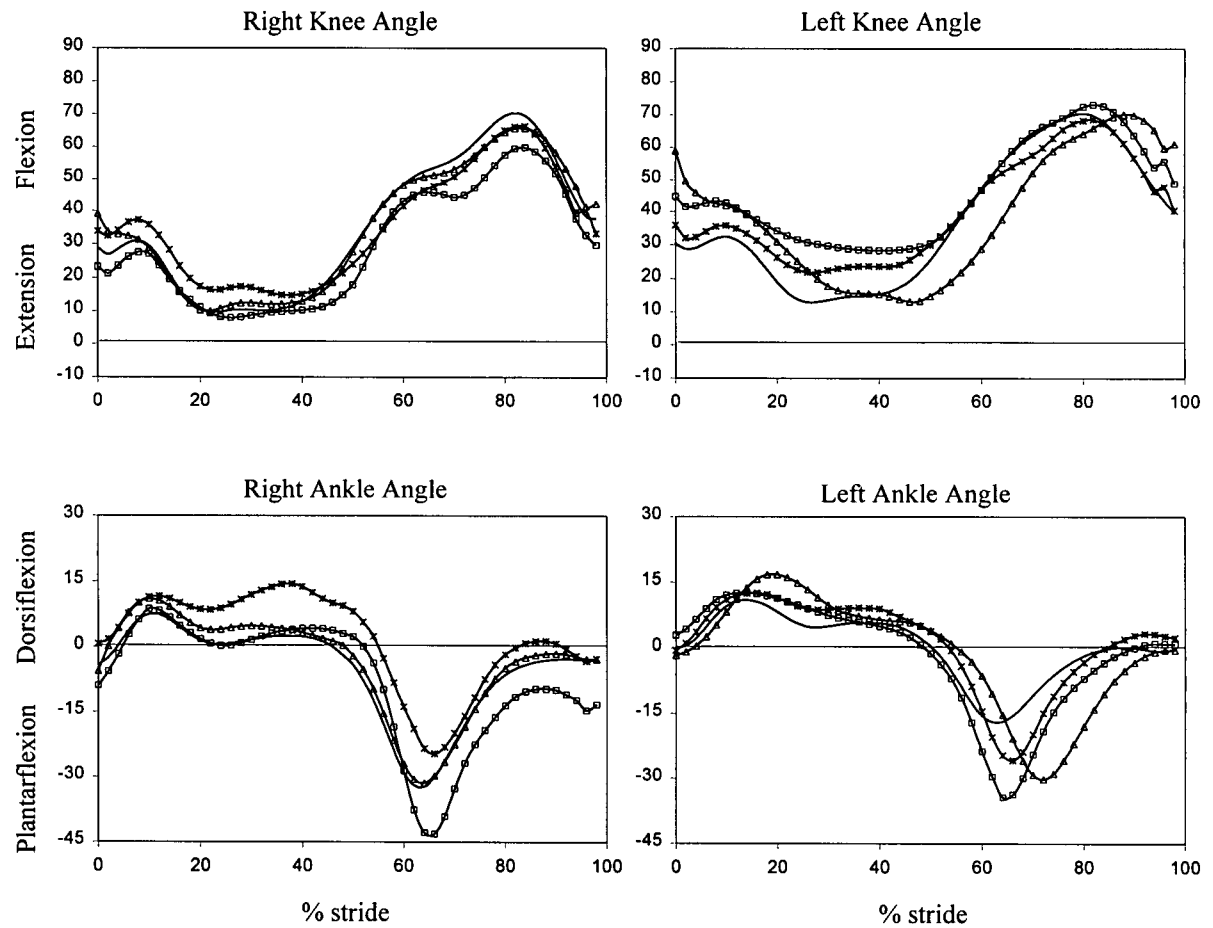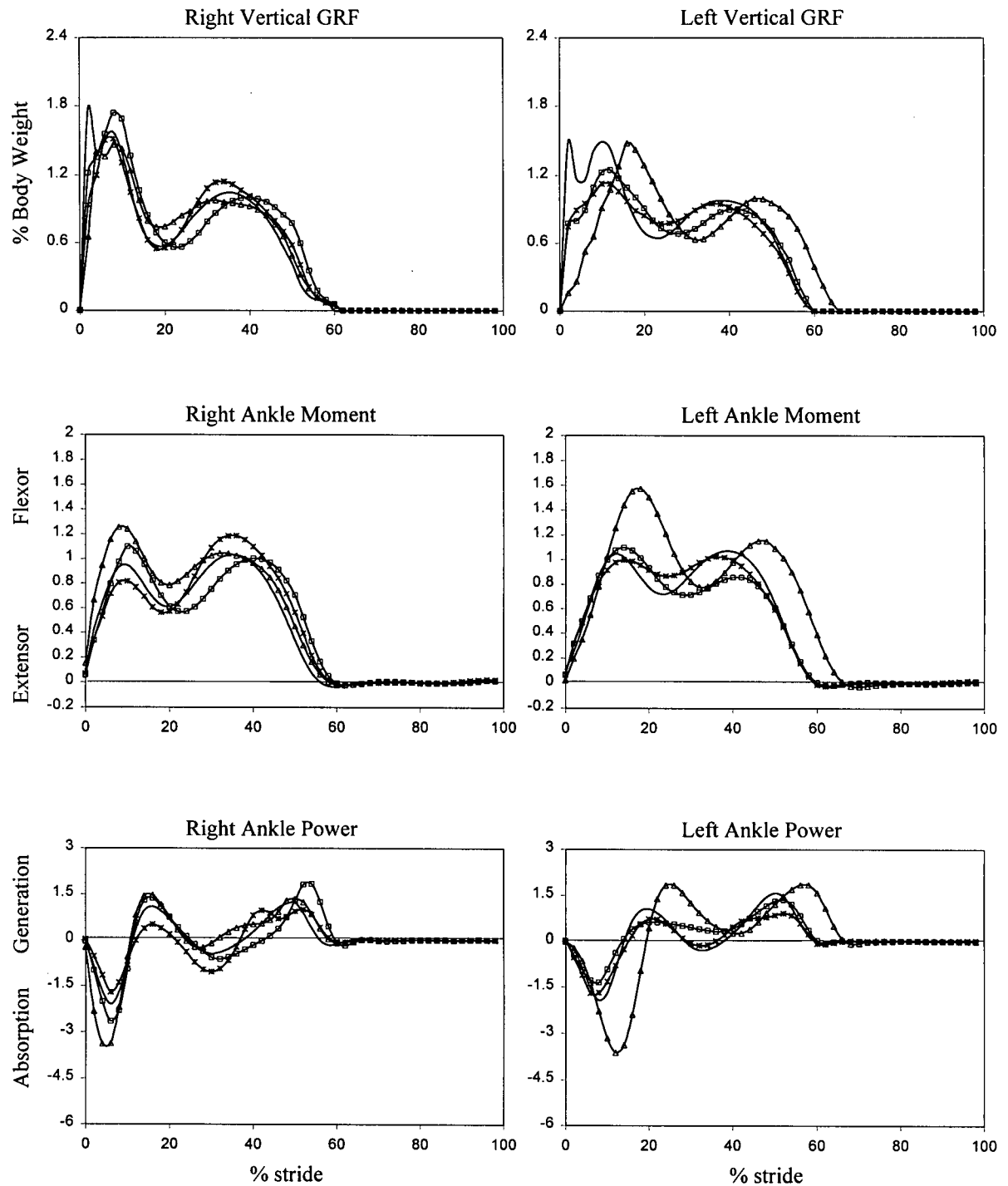
Pre     wk8     wk18     wk24

## C.6    SUBJECT 6: BTX

*Gait Kinematics*
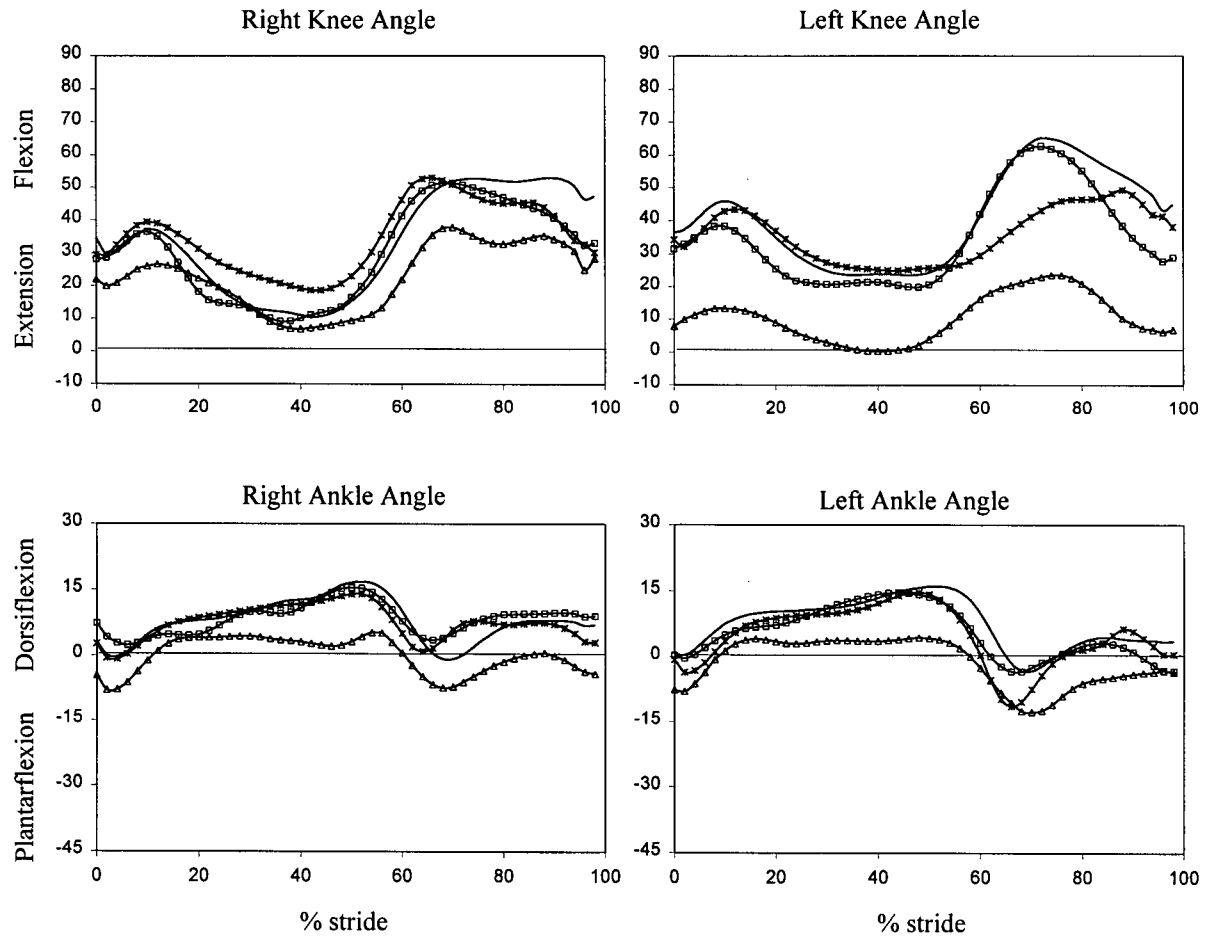


Right Knee Angle    Left Knee Angle

Right Ankle Angle    Left Ankle Angle

% stride    % stride

Pre    wk8    wk18    wk24

*Muscle Lengths*



Right Soleus

Left Soleus

Right Gastrocnemius

Left Gastrocnemius

% stride          % stride
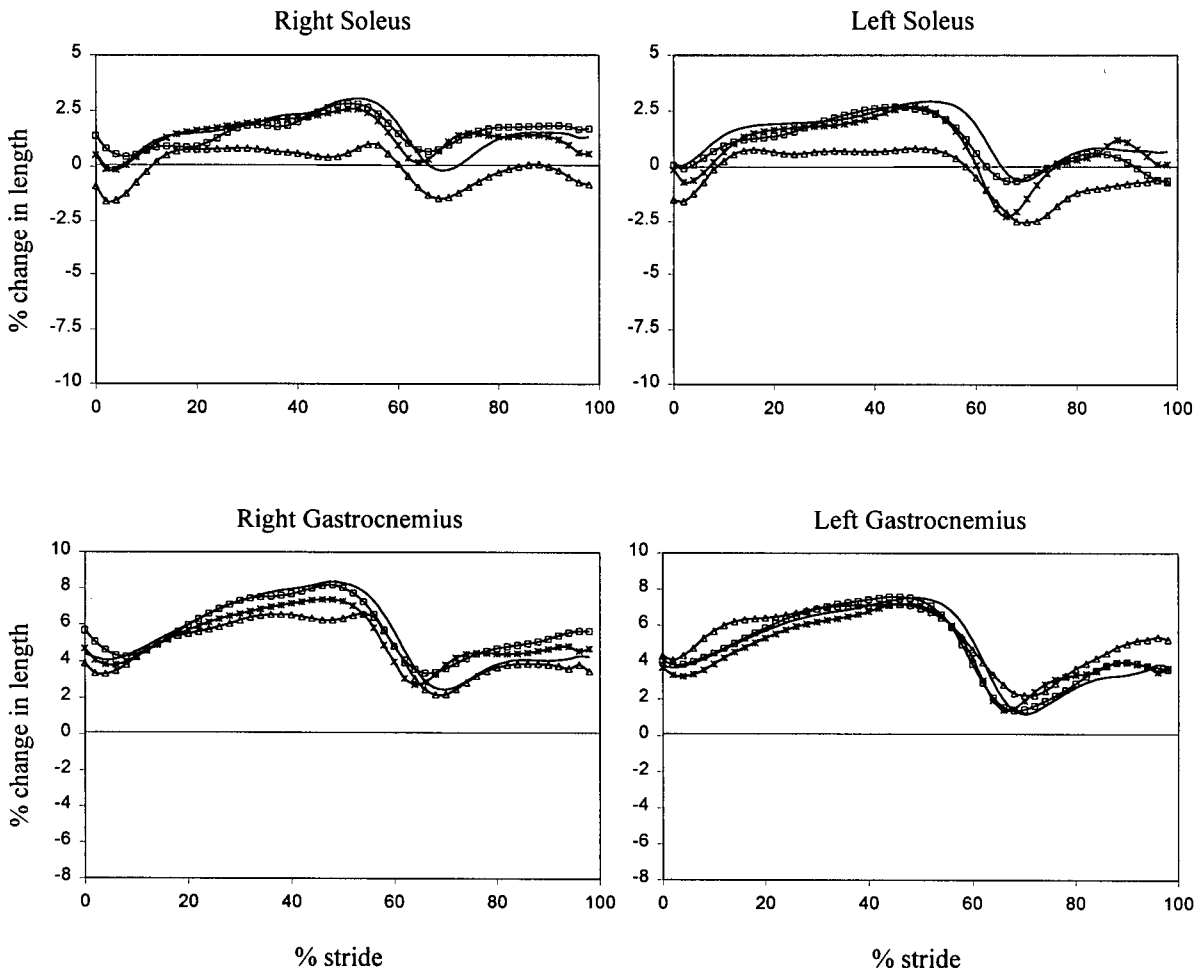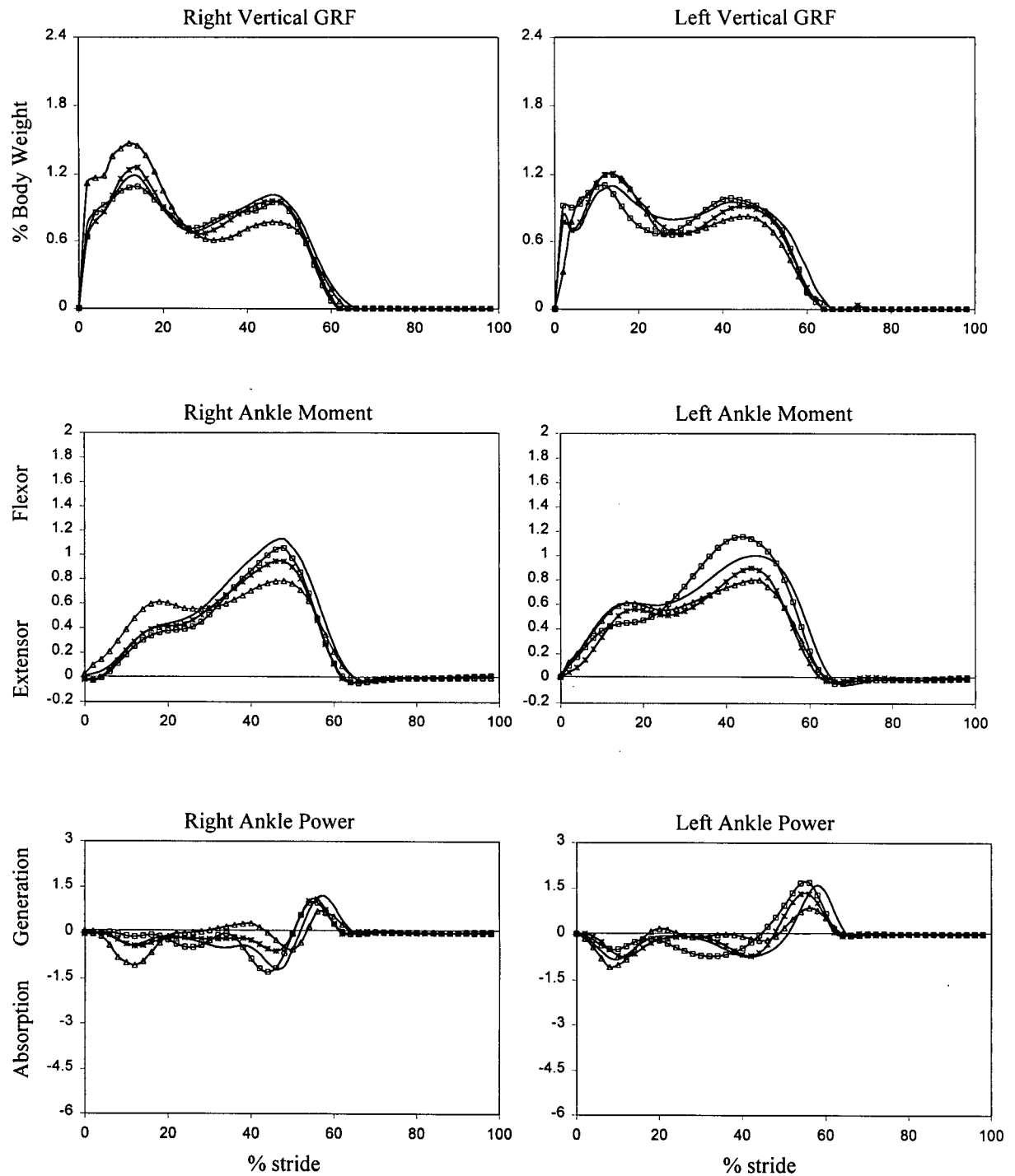
Pre    wk8    wk18    wk24

*Gait Kinetics*

## C.7    SUBJECT 7: BTX + CASTING

*Gait Kinematics*



Right Knee Angle

Left Knee Angle

Right Ankle Angle

Left Ankle Angle

% stride

% stride

——— Pre      —△— wk8      —□— wk18      —✳— wk24

*Muscle Lengths*



Right Soleus

Left Soleus

Right Gastrocnemius

Left Gastrocnemius

% change in length

% stride

——— Pre  —△— wk8  —□— wk18  —✳— wk24

*Gait Kinetics*



Right Vertical GRF

Left Vertical GRF

Right Ankle Moment

Left Ankle Moment

Right Ankle Power

Left Ankle Power

% stride

% stride
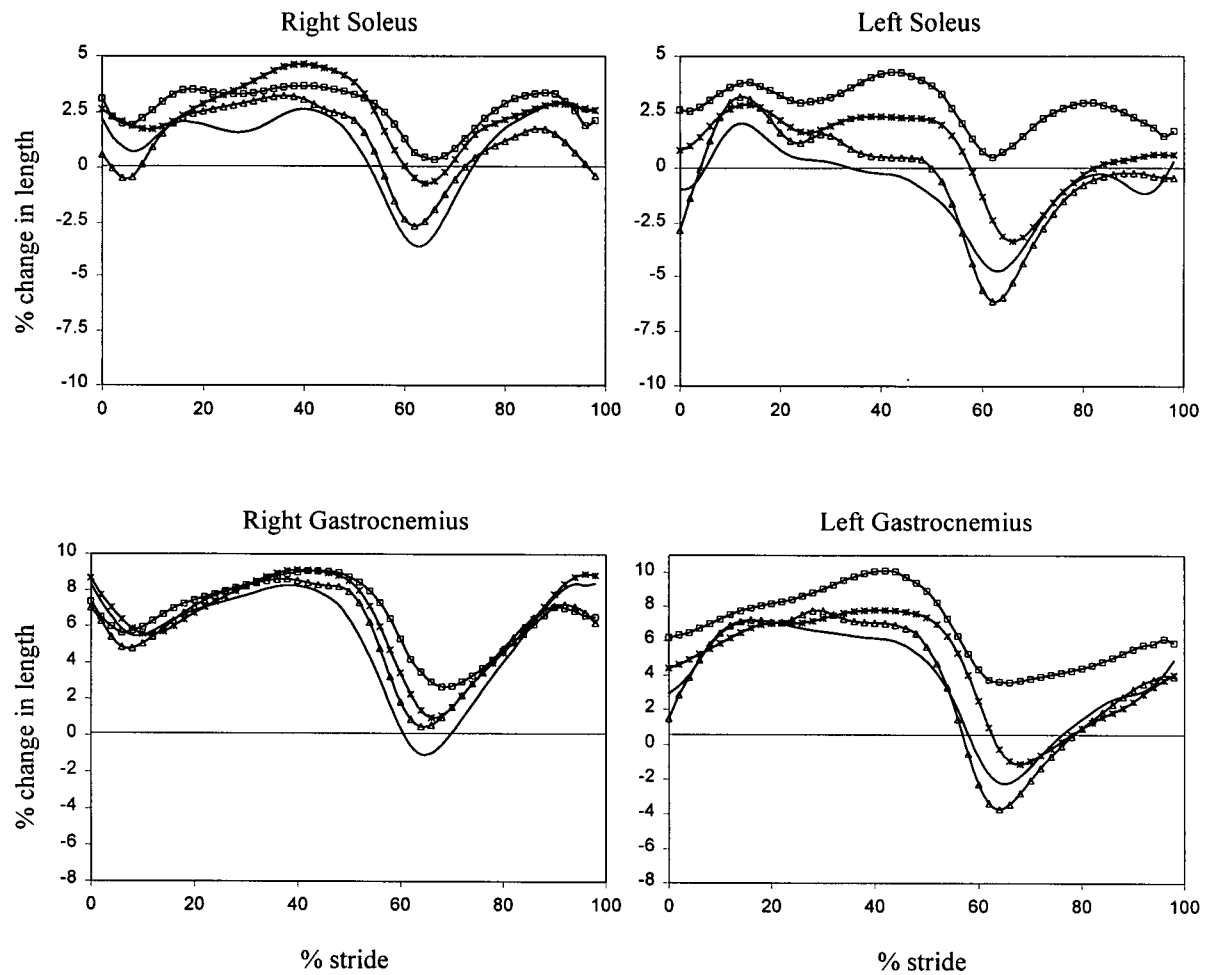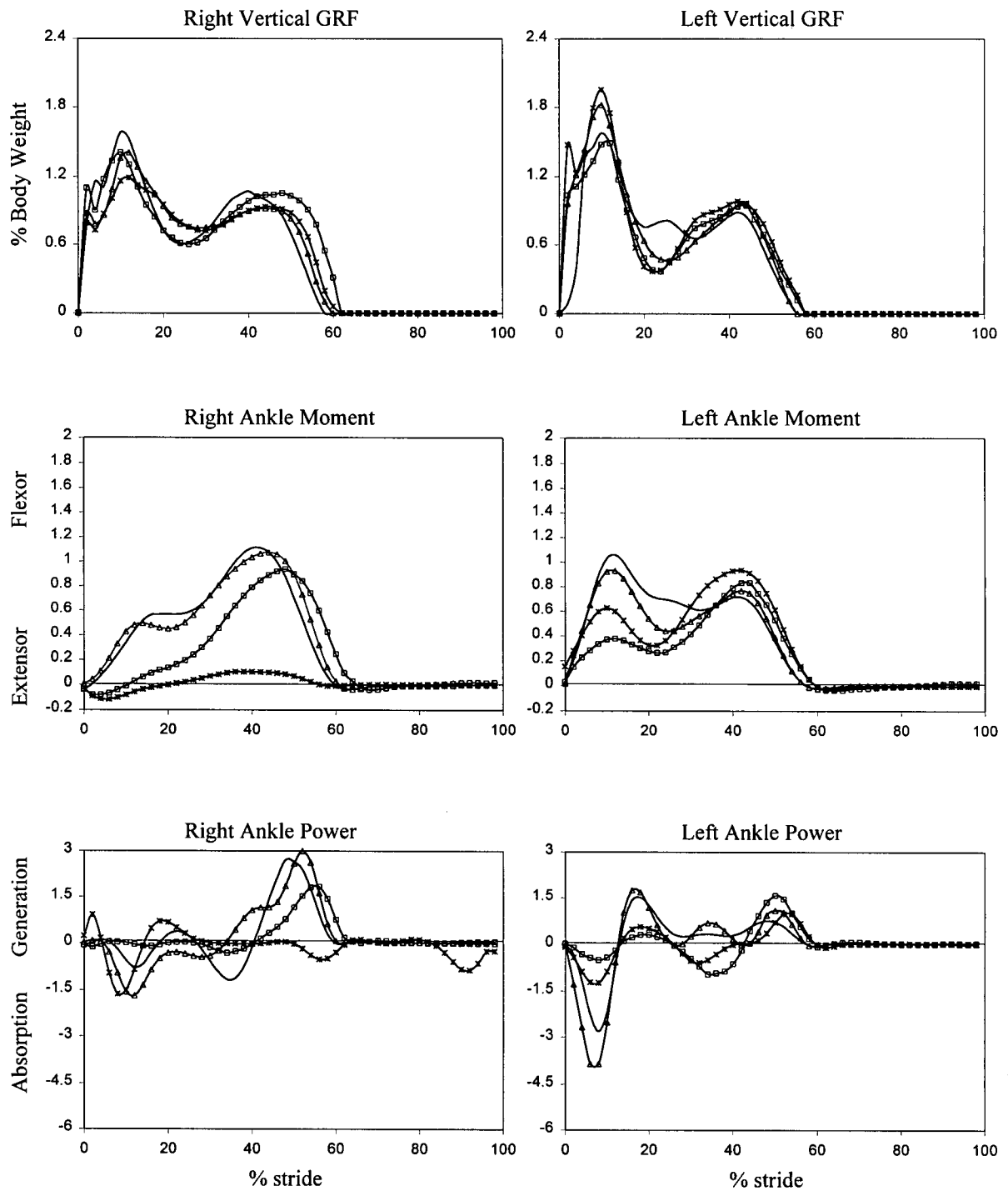
Pre     wk8     wk18     wk24

## C.8    SUBJECT 8: BTX

*Gait Kinematics*



Right Knee Angle

Left Knee Angle

Right Ankle Angle

Left Ankle Angle

% stride

% stride

Pre    wk8    wk18    wk24

*Muscle Lengths*



Right Soleus | Left Soleus | Right Gastrocnemius | Left Gastrocnemius

% change in length vs % stride

Pre — wk8 — wk18 — wk24

*Gait Kinetics*



Right Vertical GRF

Left Vertical GRF

Right Ankle Moment

Left Ankle Moment

Right Ankle Power

Left Ankle Power
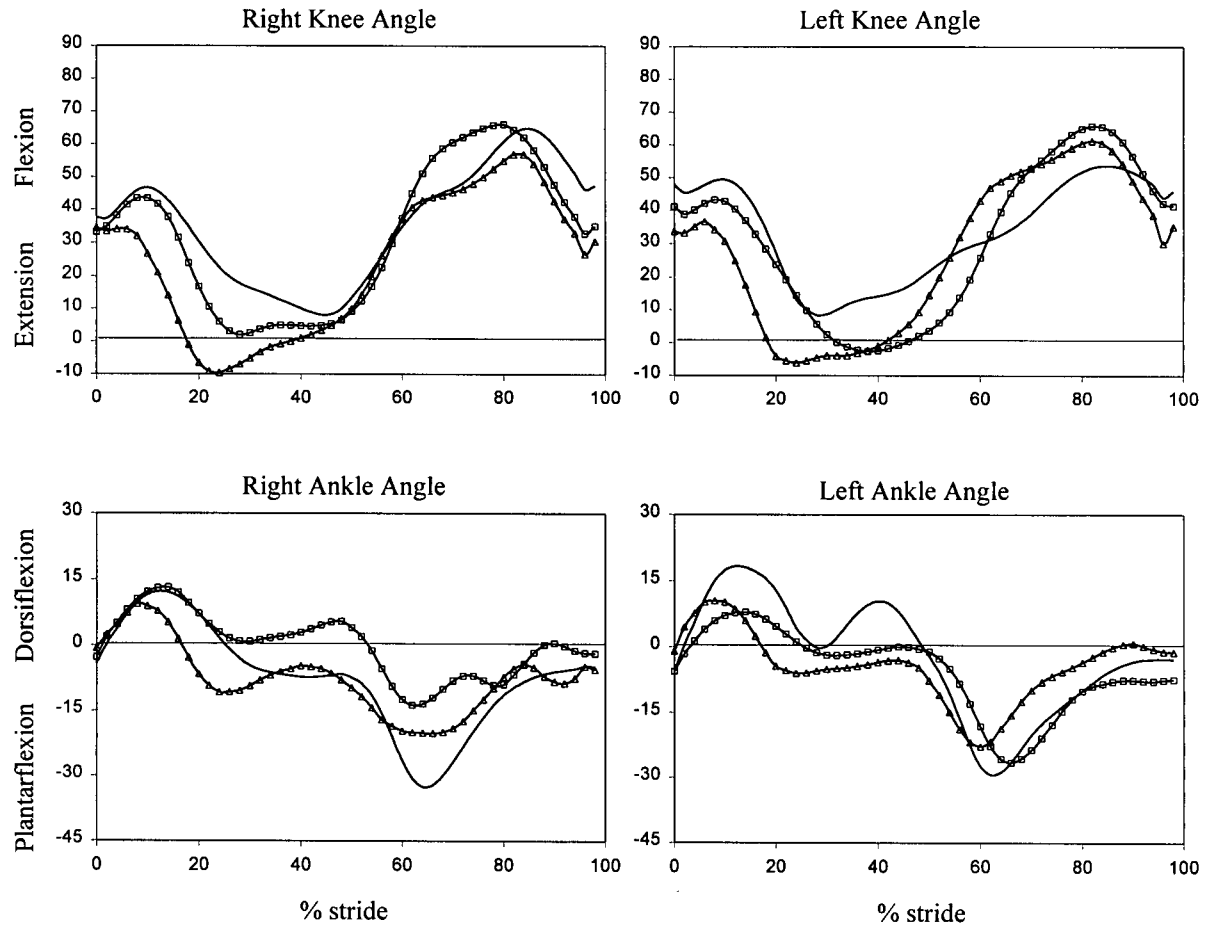
Pre ——△—— wk8 ——□—— wk18 ——✳—— wk24
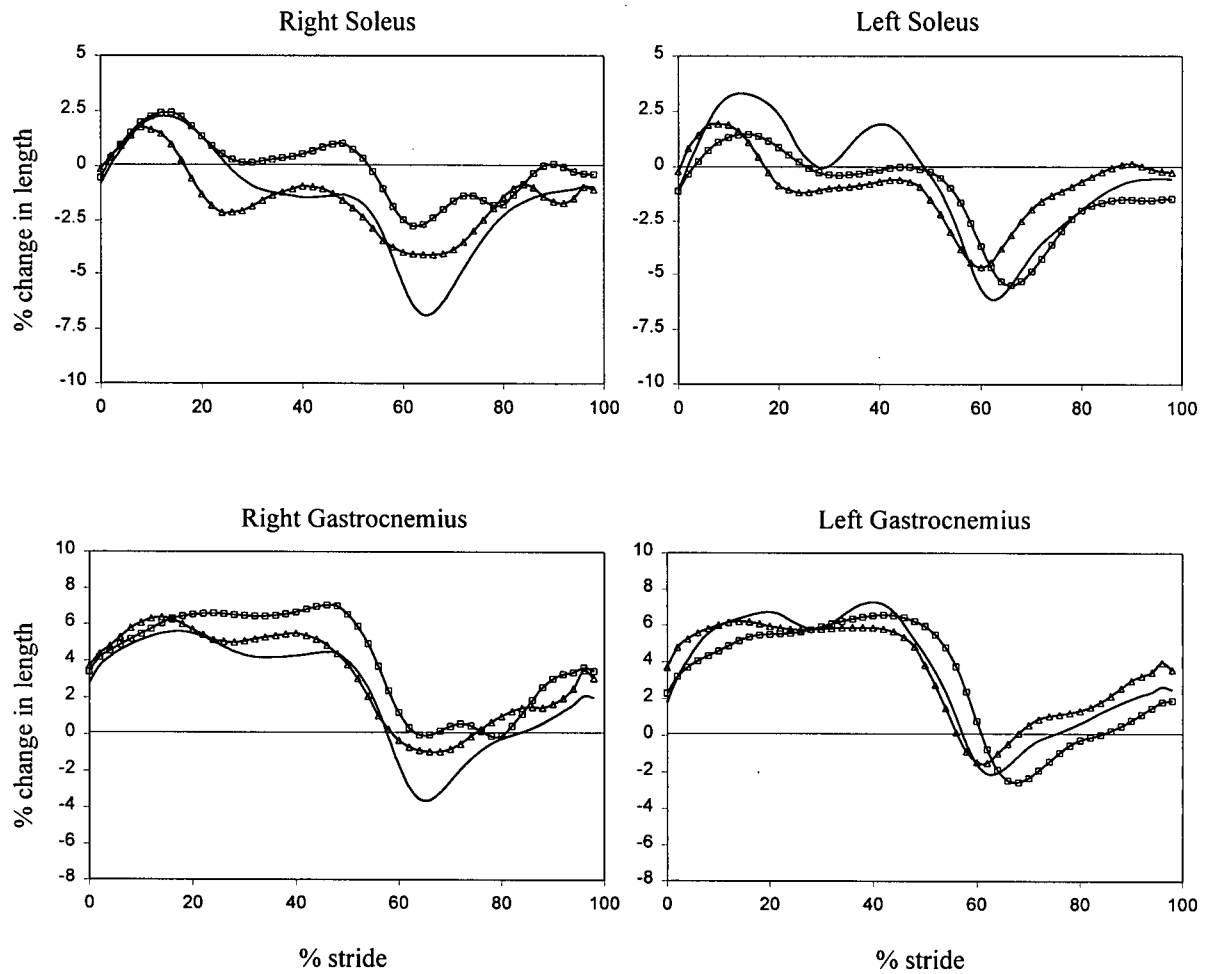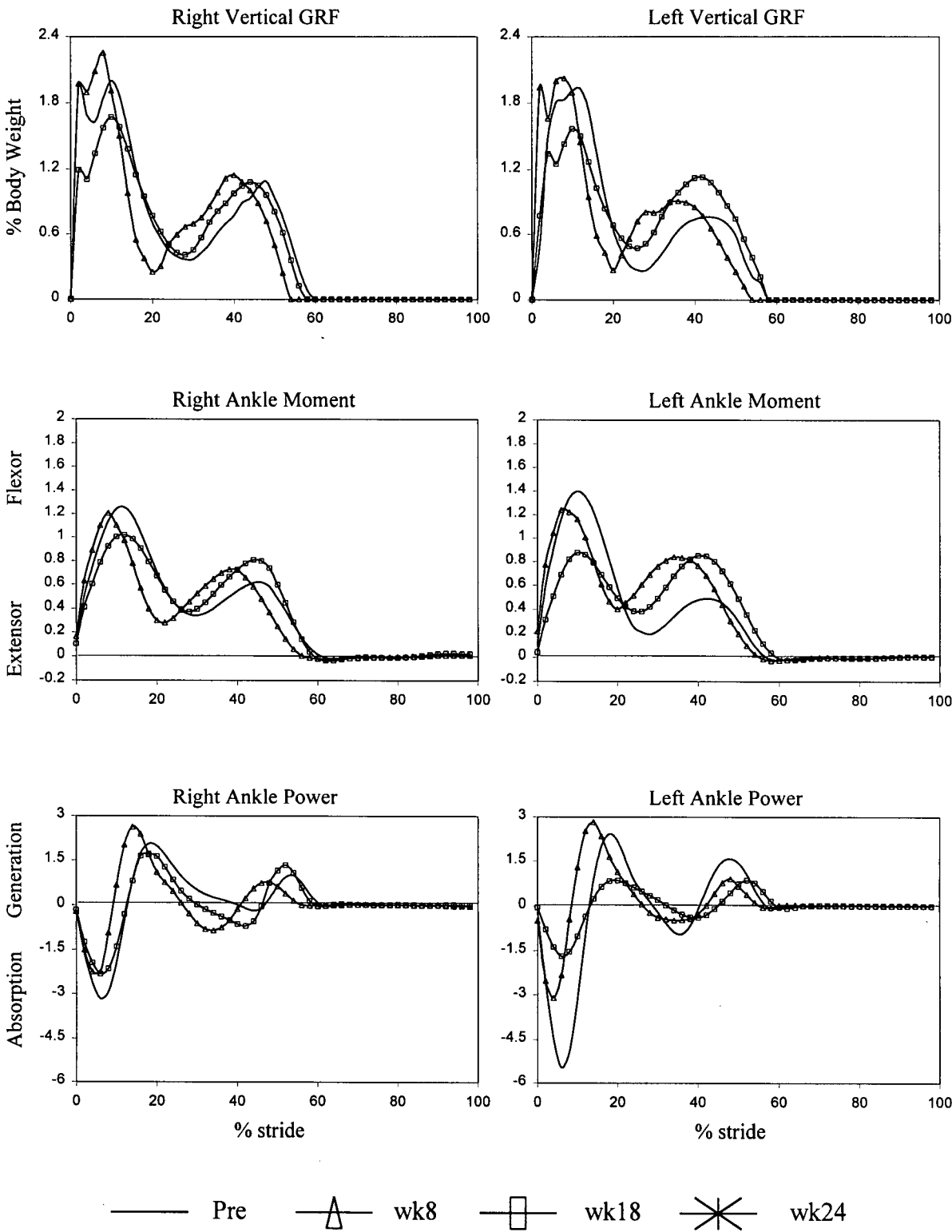
decreasing the muscle imbalance across the ankle joint which may allow more opportunity for increases in muscle length.

**Study Procedures:**

There will be 4 testing sessions in total: immediately pre-intervention, and at 8, 18, and 24 weeks post treatment. There will be three parts to each testing session: determination of spasticity of the calf muscles, determination of passive range of motion at each ankle joint, and a gait analysis. In participating in this study, your child will be required to have 3 additional gait analyses (at 8, 18 and 24 weeks post treatment) in addition to the normal treatment (which would be a pre-assessment gait analysis and the treatment itself). Your child will have to commit approximately 1-2 hours for the treatment plus an additional 1 - 1.5 hours per gait assessment for a total of 7-8 hours.

Muscle spasticity will be measured using a device specifically designed to measure the spasticity in the muscles of the calf. To measure spasticity, your child will be comfortably seated with his/her left then right foot strapped onto a footplate. The device will then move the ankle at different speeds and a measure of ankle spasticity recorded. This device will also measure passive range of motion at each ankle joint.

For the gait analyses, 21 reflective markers will be placed over various anatomical locations with adhesive tape and your child will be asked to walk across the gait lab a number of times. Six cameras will pick up the path of the markers as your child walks over a series of 2 flush-mounted force platforms.

Your child will receive a treatment after the first testing session. The method of treatment your child will receive will be randomly determined. Your child has an equal chance of receiving one of the three following treatments: serial casting alone, BTX-A alone, or a combination of serial casting and BTX-A.

For those children receiving serial casting, fibreglass walking casts will be applied to the affected legs and the foot moulded into a neutral position. After 2 weeks, new casts will be applied which will be removed after another 2 weeks, for a total of 4 successive weeks of casting.

For those children receiving botulinum toxin (BTX-A) injection, an oral sedative (Versed/Chloral Hydrate) will be administered and the injection site will be pre-treated with EMLA cream, a local anaesthetic, to decrease discomfort caused by the needle. The appropriate dosage of BTX-A will be determined according to your child's body mass (8 Units/kg). Under appropriate sterile technique, a needle will be placed into the calf muscle and the BTX-A (BOTOX® Allergan, Irvine CA) will be injected.

For those children in the combined treatment, two weeks after the BTX-A has been injected, fibreglass walking casts will be applied as outlined above, for a total of 4 consecutive weeks.

**Exclusions:**

Check any statements which apply to your child:

❑ My child is between the ages of 5-9 years old.
❑ My child has been diagnosed with spastic diplegia/spastic cerebral palsy.
❑ My child has been diagnosed with spastic calf muscles.
❑ My child can walk independently.
❑ My child has not had surgery to lengthen his/her calf muscles.
❑ My child has no known allergy to botulinum toxin.
❑ My child is not currently taking aminoglycoside antibiotics or streptomycine.  If
    unsure, list any medications your son/daughter is currently taking.

_____

_____

_____

_____

_____


**Risks:**

*BTX-A*
Side effects may occur with BTX-A injection.  The most common side effect is localized
pain due to the injection.

| Side effect | Percentage effected (n=215) |
| --- | --- |
| Leg pain | 2.3% |
| General weakness | 2.3% |
| Leg cramps | 1% |
| Fever | 1% |
| Lethargy | 1% |
| Ankle pain | 1% |
| Knee pain | 1% |
| Pain at injection site post treatment | 1% |

There has been 1 case of systemic toxicity reported in an adult male who received 1800
Units/kg intramuscularly into his neck and back over an 11-week period. The BTX-A had
leaked throughout his body causing partial temporary paralysis in muscles distant from
the injection sites.  However, the entire content of 1 of the vials that will be used in this
study is below the estimated dose for systemic toxicity in humans with a mass of 6 kg or
greater.

The BTX-A used in this study contains a small amount of human albumin therefore
infectious diseases due to the transmission of infective agents cannot be totally excluded.

However, there have been no reports of infectious disease contracted through the use of BTX-A.

*Sedatives*

| Side Effect | % affected |
|---|---|
| Increased mean arterial pressure | 2.6% |
| Decreased mean arterial pressure | 6.3% |
| Increased pulse rate | 7.1% |
| Decreased pulse rate | 9.5% |
| Increased breathing rate | 11.5% |
| Decreased breathing rate | 10.8% |
| Headache | 1.3% |
| Confusion | 0.3% |
| Hiccoughs | 0.3% |
| Nausea | 0.5% |
| Vomiting | 0.5% |

*Injections*

| Side Effect | % affected |
|---|---|
| Pain/discomfort at injection site | 100% |
| Local bruising | 50% |
| Nerve/Artery injury | <1% |
| Infection | <1% |

*Serial Casting*

| Side Effect | % affected |
|---|---|
| Muscle atrophy | 50% |
| Osteopenia (decreased bone mass) | 30% |
| Pressure sores | 10% |
| Lacerations upon cast removal | 10% |

Any medications, including over the counter medication should be taken only with the knowledge and approval of Richard Beauchamp.

Any side effects should be reported immediately to Richard Beauchamp (875-2161).

**Consent:**

I understand that my child's participation in this study is entirely voluntary and that I or my child may refuse to participate or withdraw from the study at any time without any consequences to my child's continuing medical care.

I have received a copy of this consent form for my own records.

I consent / I do not consent (circle one) for my son/daughter to participate in this study.

_____          _____
Parent/Guardian Signature                              Date


_____          _____
Witness Signature                                            Date


_____          _____
Investigator's Signature                                   Date