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DOCTORAL THESIS

NEURO BIOMECHANICAL PRINCIPLES IN ROBOT-ASSISTED GAIT TRAINING FOR PEDIATRIC PATIENTS

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I declare that I have prepared the doctoral thesis entitled: 'Neuro Biomechanical principles in robot-assisted gait training for pediatric patients' myself. All literature and information sources that I used to write this doctoral thesis were cited in the footnotes and listed in the source list.

In Prague   Dragana Žarković, MSc.

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This work is dedicated to my beloved family.

ABSTRACT

Title: Neuro Biomechanical principles in robot-assisted gait training for pediatric patients

Background: There is a lack of data on how robot-assisted gait training (RAGT) contributes to gait changes in children with cerebral palsy (CP).

Methods: This research study investigated efficacy of a 4-week RAGT intervention in twelve ambulatory spastic diparesis children with CP (10.8 ± 2.6 years old; 2 girls and 10 boys; Gross Motor Function Classification System I-III) by using computerized gait analysis (CGA); passive joint range of motion (PROM); selective control assessment of lower limbs evaluation (SCALE), and the six-minute walk test (6MWT). Pre-post RAGT intervention data of children with CP was compared with the normative data curves of typically developing children by cross-correlation, and further statistically evaluated by a Wilcoxon test.

Results: Significant pre-post RAGT intervention differences ($p < 0.05$) that indicate more physiological gait comparing to the normative data curves were found. Biceps femoris, rectus femoris, and tibialis anterior decreased activity almost across all gait cycle phases. Medial gastrocnemius decreased activity mainly in terminal stance, mid-swing, and terminal swing phases. Internal hip rotations and foot progress angles decreased almost across all gait cycle phases. More economic energy expenditure was observed in spatiotemporal gait parameters. No significant changes were observed in kinetics. Decreased joint contractures were observed in all joints, except for the popliteal angles. SCALE scores improved by at least one point and children increased walked distance by 75 meters in the 6MWT.

Conclusion: The key findings of the research study suggest that RAGT as monotherapy can induce more physiological muscle activity and joint kinematics trajectories, more economic energy expenditure in spatiotemporal gait parameters, increased SVMC ability, walking farther distances, and decreased joint contractures in CP children with spastic diparesis.

Keywords: Cerebral palsy, motor control, gait, computerized gait analysis, robot-assisted gait training, Lokomat, joint range of motion, six-minute walk test

CONTENT

LIST OF USED ABBREVIATIONS

Biceps femoris (BF)

Body weight support (BWS)

Central nervous system (CNS)

Central pattern generator (CPG)

Cerebral palsy (CP)

Computerized gait analysis (CGA)

Center of pressure (COP)

Corticospinal tract (CST)

Cross-correlation (CC)

Effect size (ES)

Electroencefalograhpy (EEG)

Gait cycle (GC)

Gross Motor Function Classification System (GMFCS)

Ground reaction forces (GRF)

Initial contact (IC)

Initial swing (IS)

Less impaired limb (LIL)

Less impaired side (LIS)

Loading response (LR)

Magnetic resonance imaging (MRI)

Medial gastrocnemius (MG)

Midstance (MDST)

Midswing (MSW)

More impaired limb (MIL)

More impaired side (MIS)

Normalized cross-correlation (NCC)

Passive range of motion (PROM)

Principal investigator (PI)

Pre-swing (PSW)

Range of motion (ROM)

Rectus femoris (RF)

Robot-assisted gait training (RAGT)

Selective Voluntary Motor Control (SVMC)

Selective Control Assessment of the Lower Extremity (SCALE)

Six-minute walk test (6MWT)

Spatiotemporal parameters (STP)

Surface EMG for Non Invasive Assessment of Muscles (SENIAM)

Surface electromyography (sEMG)

Tibialis anterior (TA)

Terminal stance (TS)

Terminal swing (TSW)

Therapy protocol (TP)

University Rehabilitation Institute of Republic Slovenia - Soča (URIS)

1. INTRODUCTION

Cerebral palsy (CP) represents arguably the most common congenital disorder often used to describe a group of syndromes that develop due to pre-existing damage or disturbances in the developing brain. CP affects motor control resulting in a limited activity that is attributed to non-progressive disturbances occurring in the fetal or infant brain. Furthermore, CP can manifest into various levels of sensory, mental, or other developmental deficits, which are most likely non-progressive, but often varying during the child's development. Children with CP benefit from intensive physiotherapy enhancing motor development to achieve independent walking. Although some forms of CP can achieve independent or partially independent walking, walking manifests itself as pathological accompanied by a lack of selective voluntary motor control, restricted joint range of motion, spasticity, and inability to walk farther distances. According to the latest research, task-specific training and physiotherapy induce functionally relevant plastic changes in the brain, and it seems to be an effective way of addressing motor symptoms, as brain plasticity in the human locomotor networks seems to be task-dependent.

Robot-assisted gait training (RAGT) is considered one form of task-dependent training which enhances the motor development of children with CP. Although manual assistance can be used to aid children with CP, RAGT allows for more advanced and customizable gait rehabilitation programs. RAGT consists of bilateral robotic orthoses, body-weight support (BWS), and a treadmill. Being a computerized system, it is possible to adjust the amount of BWS to maintain extended posture and provide accurate loading of the lower limbs. The robotic orthoses guide a patient's

leg movements throughout repeatable predefined trajectories of lower extremities. Considering the structure and function of RAGT devices, the main aim of RAGT is to improve the motor learning process through repetitive stimulation of gait accompanied by audio-visual feedback RAGT provides a simplified and safe therapeutic environment that allows for prolonged training duration with many repetitions of steps, while inducing a reproducible, kinematically consistent, symmetrical gait pattern.

This doctoral thesis represents the research study that investigated whether RAGT can contribute to the improved quality of gait patterns in children with CP. First, the doctoral thesis guides readers through theoretical frameworks of motor control principles in gait and CP to understand better the underlying problem of pathological gait in children with CP. The methodology part explains the RAGT intervention program and all procedures used to track the motor changes that can affect the quality of gait patterns in children with CP. Finally, the results are discussed and interpreted concerning clinical relevance for children with CP.

2. THEORETICAL FRAMEWORKS ON HUMAN MOVEMENT AND GAIT

2.1. Fundamentals of human movement

Human movement is a complex process that embraces the participation of different motor centers and levels of motor control. The motor cortex is responsible and involved in planning, controlling, and executing voluntary movements. The motor cortex is located in the frontal lobe and can be divided into three areas (Rosenbaum, 2009; Campbell, 2013):

1. *The primary motor cortex generates neural impulses that pass to the spinal cord and controls the execution of movement.*
2. *The premotor cortex prepares the movement phase, responsible for sensory and spatial guidance of movement, and directly controls the movement of trunk muscles.*
3. *The supplementary motor area is responsible for movement planning and sequences of the movement, coordination between 2 hemispheres (e.g. bi-manual coordination).*

2.2. Motor control

Motor control embraces the activation and coordination of muscles and extremities involved in motor performance and requires cooperation between the central nervous system (CNS) and the musculoskeletal system. Motor control subdivides into three different levels (Rosenbaum, 2009).

2.2.1. Segmental level of motor control

The segmental level represents the lowest level of motor control hierarchy and consists of reflexes and spinal cord circuits. These control automatic movements of specific groups of muscle fibers. This level of motor control includes circuits responsible for locomotion and repetitive motor activity - the so-called 'central pattern generator' (CPG) (MacKay-Lyons, 2002). CPG assumes spinal networks, which generate rhythmic and repetitive activity for locomotion without any external feedback or supraspinal control (Marder and Bucher, 2001; Mishra et al., 2013). CPG models assume that each extremity is governed by a separate neural network, whereas inter-limb coordination is achieved by coupling neural networks together. Each neural network comprises multiple unit burst generators that directly control the muscle activities of a limb. One joint is surrounded by the antagonist and agonist muscles driven by two different units. Units communicate through reciprocal inhibitory synaptic interactions (Dimitrijevic et al., 1988; Harris-Warrick, 2010).

2.2.2. Supra-spinal level of motor control

The supra-spinal level directly controls the spinal cord and comprises of two systems:

- direct (pyramidal system)
- indirect (multi-neuronal system)

Direct system

The pyramidal system represents the efferent bundle of motor neurons that originate in the sensorimotor area of the cerebral cortex, descends through the internal capsule and into the brain stem to synapse in the spinal cord. The corticospinal tract (CST) is a part of the pyramidal system, and it is an essential white matter motor pathway. The CST originates in the primary motor cortex, premotor cortex, supplementary motor areas, somatosensory cortex, parietal lobe, and cingulate gyrus. The CST comprises axons that carry movement-related information from the cerebral cortex to the spinal cord. Axons of CST neurons mainly control distal parts of extremities that perform fine voluntary movements (Levy et al., 2000). It has been proven with functional neuroimaging of human walking that the premotor cortex and the supplementary motor cortex are active before step onset (Huppert et al., 2013). Corticospinal inputs enhance muscular responses in the lower extremities during the swing phase of the gait cycle (Pijnappels et al., 1998; Xu et al., 2015).

Indirect system

The indirect system includes brain stem motor nuclei and all other motor pathways except pyramidal pathways. Axons of these motor pathways control reflex and CPG-controlled motor actions (Berne and Levy, 2000).

2.2.3. Cortical level of motor control

The cerebellum and basal nuclei represent the highest level of the motor control hierarchy. Cerebellum receives inputs and provides feedback to optimize motor activity through the projection areas of the brain stem, and motor cortex through the thalamus. Basal nuclei receive inputs from all cortical areas and send their output back to the premotor and prefrontal cortical areas through the thalamus (Bostan and Strick, 2018).

2.3. Involvement of locomotor regions during gait

Locomotor regions from mid-brain and reticular formation generate and maintain the rhythm of walking (Takakusaki, 2017). Subsequently, the proprioceptive feedback is integrated and distributed by the cerebellum, vestibular somatosensory cortex and basal ganglion. The brain stem regions signalize to spinal cord motor neurons to initiate the alteration between swing and stance phases (Kiehn, 2016).

2.4. Selective voluntary motor control

Optimal motor performance requires precision, coordination, speed, and versatility. Those are characteristics of physiological walking (Takakusaki, 2017). Selective voluntary motor control (SVMC) is essential for physiological gait, same as functional muscle groups that asynchronously alter their timing and intensity in the stance and swing phase of the gait cycle (GC). During gait, muscles are selectively activated based on their contributions to movement in all three planes and across multiple joints (Perry, 2010). Although gait is initiated voluntarily, it is stored and performed subconsciously. Each muscle is activated at a specific time and at a selected intensity to control the path of extremity.

To initiate the purposeful movement, the motor control system must know the current position of each joint in the extremity and position of the body to select appropriate muscles. Furthermore, the motor control system must be aware of the ongoing changes in the postural relationships of extremity segments to complete the movement. Position and motion awareness of each extremity and body are essential to selective control. This information is provided by the kinetic sensory system. Although the movement results from many interactions in the CNS, the CST remains the main responsible path generating voluntary and purposeful movements (Perry, 2010). The US National Institutes of Health Pediatric Motor Disorders Taskforce defined reduced SVMC as 'impaired ability to isolate the activation of muscles in a selected pattern in response to demands of a voluntary posture or movement' (Sanger et al., 2006). Reduced SVMC ability is common in children with CP (Fowler et al. 2010; Cahill-Rowley and Rose, 2013).

2.5. Fundamentals of gait

Walking is described as repetitive motion sequences motions that simultaneously move the body forward while maintaining stability (Bianchi et al., 1998; Perry, 2010). The center of body mass vaults over the supporting extremity like an inverted pendulum during each step. Some researchers describe human walking as controlled falling. At slow speeds walking is characterized by static stability when the center of body mass remains within the polygon of support formed by the extremities in contact with the ground (Lacquaniti et al., 1999; Perry, 2010). At faster speeds, dynamic stability is maintained due to the summation of the support forces, momentum, and inertial forces. During progression, the system has to maintain balance and limit energy expenditure. The mechanism for energy conservation

during walking relies on the exchange between the forward kinetic energy and the gravitational potential energy of the center of body mass as this point decelerates in the forward direction when rising and accelerates in the forward direction when falling. Muscles must perform work to replace the energy lost as heat. Additionally, the mechanism for energy recovery depends on the elastic storage in muscles and tendons. As the body moves forward, one extremity serves as a mobile source of support while the other extremity advances to a new support site (Cavagna et al., 1977; Perry, 2010). Subsequently, extremities switch their roles. A sequence of these functions performed by one extremity is called a gait cycle (GC) (Perry, 2010).

2.5.1. Gait cycle

GC starts at the moment when one foot touches the floor and stops as the same foot comes into contact for the next step. GC can be divided into stance and swing phases. Normal distribution of the floor contact periods approximates 60% for stance and 40% for swing. GC can be categorized into eight phases: initial contact (IC), loading response (LR), midstance (MDST), terminal stance (TS), pre-swing (PSW), initial swing (IS), midswing (MSW), and terminal swing (TSW). During gait, the weight-bearing extremity accomplishes four distinct functions:

- upright stability that is maintained despite postural changes

- a progression that is generated by the interaction of selective postures, muscle force, and tendon elasticity

- minimization of the impact of the shocks

- energy optimization and conservation
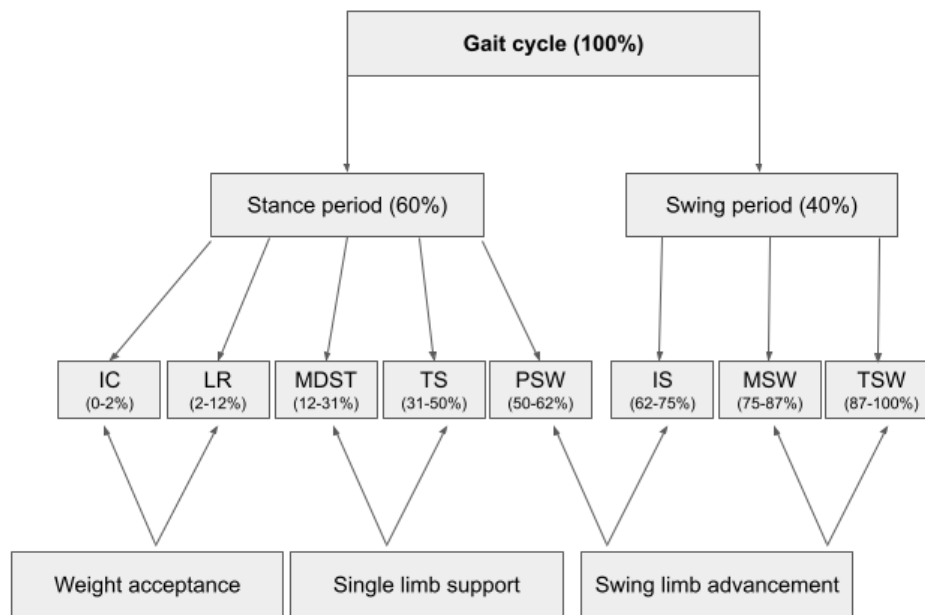
Figure 1: Functional division of the GC by foot contact. Each phase is determined by limb postures. The tasks show the phases grouping by the functions to which they contribute. (source: adapted from Perry, 2010). *Legend:* initial contact (IC), loading response (LR), midstance (MDST), terminal stance (TS), pre-swing (PSW), initial swing (IS), midswing (MSW), and terminal swing (TSW).

2.5.2. Explanation of individual phases of the gait cycle

IC includes the instant foot drop on the floor and the immediate reaction to the onset of body weight transfer. Joint postures determine the loading response pattern of the extremity. LR phase follows the IC of the foot with the floor and continues until the other limb is lifted for swing. Lifting the other foot for swing begins the single-limb support interval for the stance extremity. This continues until the opposite foot contacts the floor again.

Two phases are involved in single-limb support: MDST and TS. MDST represents the first half of the single-limb support interval. It begins as the other foot is lifted and continues until body weight is aligned over the forefoot. TS completes single-limb support. It begins with heel rise and continues until the other foot strikes the ground. The weight of the body moves ahead of the forefoot throughout this phase. Subsequently, the extremity swings through 3 postures as it lifts itself, advances to complete the stride length and prepares for the next stance interval. Four gait phases are involved: PSW; ISW; MSW; and TSW. PSW begins with IC of the opposite limb and ends with an ipsilateral toe-off. PSW initiates the forward motion that is used in the swing phase. ISW begins as the foot is lifted from the floor and ends when the swinging foot is opposite the stance foot. MSW begins as the swinging foot is opposite the stance limb. The phase ends when the swinging limb is forward and the tibia is vertical. TSW begins with a vertical tibia and ends when the foot strikes the floor. Limb advancement is completed as the shank moves ahead of the thigh (Perry, 2010).

2.6. Gait analysis

Computerized gait analysis (CGA) provides an objective, standardized and quantitative evaluation, which improves the understanding of gait abnormalities. CGA contributes to clinical decision-making of surgical procedures, muscle tone and spasticity management, physiotherapy, orthoses, and assistive walking devices. Furthermore, CGA is used to evaluate the clinical outcomes of the aforementioned interventions (Armand et al., 2016). The CGA is performed in a motion analysis laboratory equipped with optical motion capture systems, force plates and surface

electromyography (sEMG) to determine joint movement (kinematics), joint torque and power (kinetics), spatiotemporal parameters, and muscle activity Feng et al., 2016). A typical CGA takes between 2 to 3 hours. Patients must be able to walk at least short distances with or without assistive aids, follow simple instructions, and tolerate the placement of markers and electrodes. Patients can be tested with or without regularly used orthoses or assistive devices. Gait patterns are studied in terms of a GC gait cycle and help to identify causes of gait abnormalities (Wren et al., 2011). Motion analysis laboratories typically use available normative reference values generated by the software to detect gait deviations from physiological gait patterns. Such reference values are collected from an extensive sample and represent a reliable source. Subsequently, the software generates a CGA report which includes all variables embracing joint kinematics, kinetics, spatiotemporal parameters, and also sEMG (Frigo and Crenna, 2009; Baker, 2013).

2.6.1. Three-dimensional kinematics

Three-dimensional (3D) kinematics involves optoelectronic motion analysis systems that digitally reconstruct the individual's body as a multisegment system. 'Conventional gait model'; 'Vicon adapted model'; and the 'Vicon plug-in gait model' are the most frequently used biomechanical models for digital reconstruction (Baker, 2013). 3D kinematics describes the movements of body segments and joint centers. Construction of 3D coordinates and orientation of the rigid body segments allow for calculation of joint angles of the proximal and distal segment, joint angular velocity, and joint acceleration. Measurements are collected for each joint in all three cardinal planes of motion (Baker, 2013; Armand et al., 2016).

2.6.2. Kinetics

Kinetics explains the cause of movement presented by ground reaction forces (GRF), joint moments, and joint powers. GRF is measured with force plates embedded in the ground during CGA and refers to forces that influence the body throughout the stance phase of GC. GRF is divided into vertical, mediolateral, and anteroposterior force plots. The origin of force on the foot is termed as a center of pressure (COP). Common processing of COP, GRF, and joint kinematics allows for a calculation of joint moments. Specifically, joint moments show how GRF, inertia, and gravity interact with the internal recruitment of muscles, tendons, ligaments, and bony structures that stabilize the joint (Perry, 2010; Baker, 2013). Joint power indicates the velocity of the joint moment or the rate of the work exhibited by the muscles. Positive power values indicate energy generation and are commonly associated with concentric contractions, while negative power values signify energy absorption and are frequently associated with eccentric contractions (Perry, 2010).

2.6.3. Spatiotemporal parameters

Spatiotemporal parameters (STP) of gait can be defined as the time and space characteristics of an individual's walking pattern. STP include cadence, velocity, stride length, step length, and step width are reported based on the calculation of 3D coordinates. Cadence or walking rate is calculated in steps per minute. Velocity refers to the individual's comfortable walking speed. Stride length is the distance between successive points of IC of the same foot. Right, and left stride lengths are equal in healthy individuals. Step length is the distance between the point of IC of one foot and the point of IC of the opposite foot. Right, and left step lengths are

similar in healthy individuals. Step width was determined as the distance between the outermost borders of two consecutive footprints (Perry, 2010).

2.6.4. Surface electromyography

sEMG is an indirect method for analyzing muscle activation patterns by identification of timing and relative intensity of muscular function by recording the signals of activation. Myoelectrical signals can be recorded as they spread through the muscle and adjacent soft tissues with appropriate instrumentation (Feng, 2016). These can be observed in 8 GC phases which can be used as a reference base to provide the most functional significance for the data on muscle activity (Perry, 2010; Baker, 2013).

Although sEMG can answer several clinical questions such as:

- 'When is the muscle active?';

- 'How hard is the muscle working';

- 'How does the effort of one muscle compare to the of others?';

- 'What is the quality of the neural control',

sEMG cannot directly measure the muscle force (Armand, 2016).

2.7. Six-minute walk test

CGA can be completed with functional walk tests such as a six-minute walk test (6MWT). The test provides valuable functional information on gait abilities and therapeutic outcomes in adult and pediatric patients (e.g. children with CP). 6MWT is an easily administered, self-paced, sub-maximal walking test. The 6MWT is performed under controlled conditions in which the distance walked in 6 minutes is measured (Thompson et al., 2008). Research supports the reproducibility (intraclass correlation coefficient = 0.80) and reliability (intraclass correlation coefficient = 0.98) of the 6MWT for older independently-ambulating children and adolescents with CP (Thompson et al., 2008; Livingstone and Paleg, 2016; Fiss et al., 2019).

3. THEORETICAL FRAMEWORKS ON CEREBRAL PALSY

3.1. Definition of cerebral palsy

Cerebral palsy (CP) is a developmental disability firstly described by William Little in the 1840s. Since then, CP stills to be of the most frequent diagnoses with an incidence of 2-3 per 1000 children (Shevell and Bodensteiner, 2004; Panteliadis, 2004). CP indisputably represents the most common congenital disorder in childhood. CP is often characterized as "an umbrella term" that describes a group of syndromes developing due to pre-existing damage or disturbance in the developing brain that manifests at different levels (Panteliadis, 2004; Damiano, 2006). Manifestations of the CP include motor, sensory, mental, or other developmental deficits.

CP can be considered a form of static encephalopathy with varying clinical symptoms within the period of a child's growth, developmental plasticity, and maturation of the CNS (Becher 2002; Hankins and Speer, 2003; Sankar and Mundkur, 2005).

3.2. Etiology and risk factors of cerebral palsy

The etiology of CP is diverse and multifactorial. It includes congenital, genetic, inflammatory, infectious, anoxic, traumatic, and metabolic causes. The injury to the developing brain may occur in the prenatal, natal, or postnatal periods. Prenatal risk factors include intrauterine infections; teratogenic exposures; placental complications; multiple births; seizures; and hyperthyroidism. Perinatal risk factors are infections, intracranial hemorrhage, seizures, hypoglycemia, hyperbilirubinemia, and significant birth asphyxia. Postnatal causes include toxic, infectious meningitis, encephalitis, traumatic such as drowning. Despite the known factors causing CP, the cause of CP remains unknown (Hankins and Speer, 2003).

3.3. Diagnostics of cerebral palsy

CP is diagnosed based on awareness of risk factors, regular developmental screening of high-risk patients, and neurological examination. It is impossible to diagnose CP in infants who are younger than six months, except for very severe cases. Motor patterns and behavior of various CP forms emerge gradually. The earliest alarming signs are a delay in developmental milestones and abnormal muscle tone that may be variable in different periods or due to various emotional conditions. Once acquired developmental milestones do not show regression.

However, repeated clinical examinations and monitoring over some time are needed to confirm the CP diagnosis (Sankar and Mundkur, 2005). Complete evaluation of children with CP is based on repeated clinical examinations; monitoring over some time; electroencefalograhpy (EEG) to track history of epilepsy; magnetic resonance imaging (MRI) is needed to detect lesion precisely; genetic and metabolic tests are used to track the possible evidence of deterioration or metabolic compensation, and finally the family history of childhood neurological disorder associated with CP (Hankins, 2003). Furthermore, complex diagnostics is followed by assessments of associated deficits like impaired vision, speech and hearing, sensory profile, oromotor evaluation, and cognitive functioning (Hankins, 2003; Shevell and Bodensteiner, 2004).

3.4. Deficits associated with cerebral palsy

Mental retardation is present in up 60% of children with CP. It has been reported that children with spastic quadriplegia type of CP have a greater degree of cognitive impairment than children with spastic hemiplegia type of CP (Panteliadis, 2004; Sankar and Mundkur, 2005; Damiano, 2006). Visual impairments were reported in almost 30% of children with CP. Typically observed visual impairments include strabismus, amblyopia, nystagmus, optic atrophy, and refractive errors (Salt and Sargent, 2014). Hearing impairment affects approximately 12% of children with CP and mostly relates to CP etiology of very low birth weight, kernicterus, neonatal meningitis, or severe hypoxic-ischemic insults (Sankar and Mundkur, 2005). Between 35-65% of children with CP develop epilepsy. Children with spastic quadriplegia or hemiplegia have a higher incidence of epilepsy than children with

diplegia or ataxic type of CP (Singhi et al., 2003). Speech is affected due to bilateral corticobulbar and oromotor dysfunctions including receptive, and expressive language deficits. These are commonly associated with mental retardation. Articulation disorders and impaired speech are present in almost 40% of children with CP. Furthermore, oromotor problems, feeding difficulties, swallowing dysfunction, and drooling are present (Reilly et al., 1996). Abnormalities of proprioception and tactile sensations are common in children with CP. Psychiatric disorders include anxiety, depression, hyperkinesis, and inattention (Downs et al., 2018).

3.5. Motor deficits in cerebral palsy

The most common motor deficits in CP include lack of SVMC, primitive reflex gait patterns, spasticity, muscle weakness, contractures of soft tissues, decreased joint range of motion, and impaired balance (Chruscikowski et al. 2017). Damage to motor tracts in the periventricular white matter is a primary etiology in spastic diplegia which represents the most common type of CP (Fowler et al., 2009). Specifically, it is the aforementioned CST that is responsible for SVMC. It is suggested that the distal lower-extremity tracts are closer to the ventricle of CST and therefore are more vulnerable to perinatal damage than those of the proximal lower-extremity (Staudt et al., 2003; Fowler et al., 2009). Reduced SVMC results in involuntarily coupled primitive movement patterns that are typically observed in the lower extremity during gait. Children with CP may develop movement strategies that retain primitive coupled patterns to various degrees (Fowler et al., 2009; Fowler et al., 2010). SVMC ability may be a determining factor affecting functional movement

tasks and may indicator of improvement following interventions (Goldberg et al., 2012). SVMC can affect gait biomechanics in children with CP. This can be explained on the stance and swing phases of the gait cycle. During stance, the hip and the knee normally extend (appropriate coupling), while during the swing, the hip normally flexes while the knee extends (uncoupled movement). Children with CP are unable to dissociate hip and knee recruitment which results in reduced knee extension during a terminal swing (Farmer et al., 2008; Cahill-Rowley and Rose, 2014; Fowler et al., 2010). Mirror movements are another abnormality that occurs in children with CP. Mirror movements occur when a voluntary movement is accompanied by a simultaneous, involuntary, and identical movement on the contralateral extremity. The etiology of mirror movements is thought to be the strengthening of ipsilateral CST connections. CST connections are pruned during typical early development. Voluntary movement is driven by efferent motor signals which descend through the CST. The loss of descending control leads to abnormal input to motoneuron pools in the spinal cord. This may result in the inability to develop or maintain the complex spinal networks involved in muscle activation patterns of agonists, synergists, and antagonists (Farmer et al., 2008; Fowler et al., 2010).

3.5.1. Assessment of selective voluntary motor control

Although the clinical importance of SVMC seems obvious, it is rarely routinely assessed in the clinical environment. Development of the Selective Control Assessment of the Lower Extremity (SCALE) has allowed for reliable assessment of SVMC with an easily implemented tool. Three recent studies from the SCALE developers showed its predictive ability in relation to neurologically-induced gait

disorders (Fowler et al., 2009; Fowler and Goldberg, 2009; Fowler et al., 2010). The SCALE is the most current assessment of SVMC. It grades an individual's ability to perform isolated, voluntary joint movements of the hip, knee, ankle, subtalar, and toe joints without involving other joints in the same or contralateral legs. Scores are assigned as: normal - joints moved selectively within at least 50% of the possible range of motion (ROM) and at a physiological cadence; impaired - movement performed slower below 50% of ROM, with mirror and/or synergistic movements; or unable - no joint movement performed or synergy patterns present. SCALE scores have been found to correlate with Gross Motor Function Classification System (GMFCS) (Spearman's rank correlation coefficient 0.83, p<0.001) and had a high inter-rater reliability (interclass correlation coefficient 0.88–0.91,p<0.001) (Fowler et al., 2009; Fowler and Goldberg, 2009; Fowler et al., 2010). The SCALE assessment of SVMC is repeatable and functionally relevant (Balzer et al., 2016). The grading scale is simple and does not require equipment, and the examination of five joints per extremity is thorough.

3.6. Passive joint range of motion

SVMC is typically assessed with passive joint range of motion (PROM). Loss of joint range of motion (ROM) is a major concern in the long-term management of children with CP. It is a prevalent secondary complication of the abnormal muscle tone often associated with CP. Monitoring of joint PROM in both the upper and lower extremities is an important component of assessment and follow-up over the life span (Darrah et al., 2014). A parameter associated with the development of gait in children with CP is the lower limb joints' PROM, while its restriction often relates to

musculoskeletal deformities (Dimakopoulos et al., 2019). Indeed, most children with abnormally high muscle tone (spastic types of CP) manifest as decreased PROM and musculoskeletal deformities at some stage of their development which usually worsens as age increases. This is important, as in many cases the treatment of the restricted PROM utilizing botulinum toxin, orthotics, and orthopedic interventions contributes significantly to enhancing the movement and quality of life of children with CP (McDowell et al., 2012). Goniometry is the most frequently used clinical evaluation method of the joints' PROM in children with CP. Its' accuracy and reliability were studied extensively, and it has become an established method for evaluating PROM, with high inter-rater and intra-rater reliability (Kilgour, 2003; McWhirk et al., 2006; Berge et al., 2007; Nordmark, 2009).

3.7. Topographic classification of children with cerebral palsy

CP can be classified as paresis that stands for weakness, or plegia expressing paralysis in which all voluntary movement is lost. Furthermore, CP can be classified into four groups according to the affected body areas: monoplegia/monoparesis, diplegia/diparesis, hemiplegia/hemiparesis, and quadriplegia/quadriparesis (Panteliadis, 2004; Sankar and Mundkur, 2005; Damiano, 2006). Monoplegia is the mildest form of CP and includes impairment of a single extremity. Despite that, other types of CP may begin to manifest as monoplegia, and further develop in hemiplegia/hemiparesis or quadruplegia/quadruparesis. Spastic diplegia/diparesis is associated with prematurity and low birth weight. This type of CP predominantly affects both lower extremities. A mild form may manifest as toe walking due to impaired dorsiflexion of the ankle joints with increased muscle tone of triceps surae

muscle. Flexion of hip and knee joints accompanied by internal hip joint rotation are present in severe cases. This is due to the spasticity of hip adductors that cause scissoring of the lower extremities. Hemiplegia/hemiparesisis a form of unilateral impairment of both upper and lower extremities. However, the upper extremity is predominantly affected. Voluntary movements and fine motorics are affected the most. The lower extremity is typically affected by persistent flexion and internal rotation of the hip and equines foot position. Quadruplegia/quadruparesis represents the most severe form of CP that involves all four extremities with the predominant effect of upper extremities and trunk. These patients have severely impaired ability to perform voluntary movements (Panteliadis, 2004; Sankar and Mundkur, 2005; Damiano, 2006).

3.8. Neuromuscular deficits in children with cerebral palsy

Neuromuscular deficits in children with CP involve neuromuscular and joint-skeletal impairments such as spasticity; dystonia; joint contractures; abnormal bone growth; poor balance; loss of SVMC; and muscle weakness. Accordingly, CP can be classified as spastic, dyskinetic, ataxic, hypotonic, and mixed type. Spastic CP is the most common and accounts for 70-75% of all CP cases, dyskinetic type ranges between 10-15%, and ataxic is less than 5% of cases. Spastic type clinically manifests as loss or absence of tone in lying and increased tone in sitting, standing, or walking. The dyskinetic type of CP can be divided into the hyperkinetic (athetoid) and dystonic types. Both of the subtypes are characterized by extrapyramidal involvement due to damage of basal ganglia. The athetoid type involves involuntary movements that are most evident in the facial area and extremities during the rest.

Dystonic type manifests as slow yet powerful contractions of agonist and antagonist muscles simultaneously. The severity of dystonic movements varies with body position, emotional state, and sleep. Furthermore, there are also abnormalities of posture control and coordination. Ataxic type is the least frequent form of CP. The ataxic type of CP is caused by damage to cerebellar structures. These children lack coordination during precise movements which are followed by tremors; hypotonia; ataxia; impaired balance; and wide-based gait. Walking ability is developed in a delay. Hypotonic children with CP start to develop generalized muscular hypotonia. This type of CP generally has no cognitive impairment.

3.9. Gross motor function classification system

Palisano et al. (2000) developed the Gross Motor Function Classification System (GMFCS) to provide an objective classification of motor disability patterns in children with CP. The GMFCS objectively classifies a child's current gross motor function and focuses on the child's self-initiated movement emphasizing sitting and walking. The GMFCS is divided into five levels where children in Level I have the most independent motor function; and children in Level V have the least. The GMFCS describes the functional characteristics in five levels and across the following age groups: up to 2 years; 2-4 years; 4-6 years; and 6-12 years. Each level and age group have separate descriptions. GMFCS became one of the most frequently used prognostic and stratification systems that are routinely used in children with CP. Furthermore, this is the only reliable method of prognostication for walking ability in children with CP (Morris and Bartlett, 2004; Palisano et al., 2008).
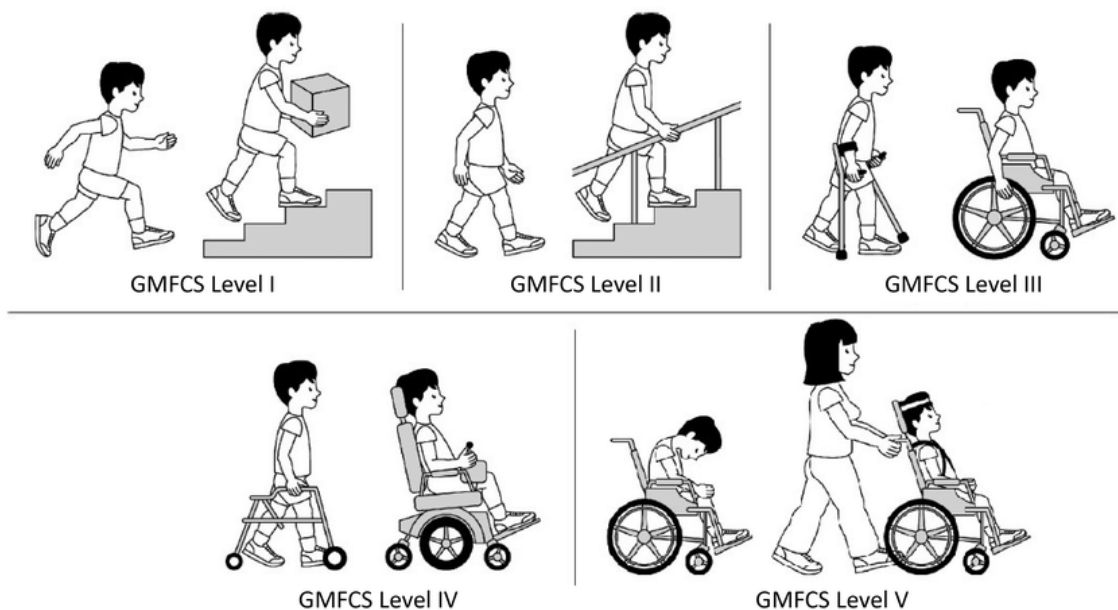
Figure 2: GMFCS descriptors (source: Palisano et al., 1997, <u>available online</u>).

3.10. Gait development in children with cerebral palsy

Generally, children with CP start to walk later than typically developing children, and some never reach an independent gait. It is important to predict whether children with CP will walk to plan appropriate therapeutic and rehabilitation goals. The vast majority of studies indicate that age at the achievement of sitting position without support is a predictor of ambulatory status (Novak et al., 2013). da Paz Júnior et al. (1994) reported that achievement of head balance before nine months, sitting by 24 months, and crawling by 30 months were predictors of the achievement of ambulation. Sala and Grant (1995) reported that primitive reflexes, postural reactions, gross motor skills, and the type of CP seemed to be the main factors in predicting the achievement of ambulation. This was further supported by Badell-Ribera's (1985) prospective study of 50 children with spastic diplegia where all children who became independent walkers achieved sitting and crawling between

18 and 30 months of age. Rosenbaum et al. (2002) described a milestone of motor development to achieve gait around the age of seven years. Despite that, children with CP fail to develop mature intra-limb coordination.

4. THEORETICAL FRAMEWORKS ON NEUROPLASTICITY

Brain injury or disease is followed by widespread biochemical, anatomical, and physiological changes. A patient's brain affected by such an injury or disease is forced to reacquire lost behaviors and relies on neural plasticity within the residual neural circuits. The same neural and behavioral signals driving plasticity during learning in the intact brain are engaged during relearning in the damaged/diseased brain (Kleim, 2011).

Early brain injury occurring in children with CP can lead to atypical brain development and reorganization, particularly during the first two years of life. This period could represent a critical window during which rehabilitation might be the most effective, but which is missed. The vast majority of available studies are conducted in school-aged children with CP. Studies showed that intensive, activity, task-specific, and goal-oriented rehabilitation improves motor function in school-aged children with CP (Araneda et al, 2020). Animal models of CP have shown that impairments due to perinatal brain injury are mainly secondary to persistent inflammation. The inflammation alters neurogenesis, axonal growth, and synaptogenesis, as well as, causing impairments within the white matter. Studies have shown that these alterations can be partially reversed in animals through early intensive motor skill learning-based interventions provided during the optimal developmental window of opportunity. Neuroplasticity is explained as the adaptive capacity of the central

nervous system (plasticity). It is also the mechanism by which the damaged brain relearns lost behavior in response to rehabilitation (Kleim, 2011). Based on the latest scientific data it is strongly suggested that neurons, among other brain cells, possess the remarkable ability to alter their structure and function in response to internal and external pressures, including behavioral training. Children with CP can improve motor function with practice (Hemayattalab and Rostami, 2010). Functional and task-oriented treatment approaches have the potential for improving motor function when implemented with adequate intensity (Gordon and Magill, 2011). Motor learning is considered critical for learning-dependent neuroplasticity and restorative therapies after neurological injury, such as stroke or CP (Winstein et al., 2014). Indeed, the acquisition of new skills is similar to re-learning of lost skills after damage to the neuromotor system (Dayan and Cohen, 2011; Chandramouli et al., 2019). A damaged brain can use either recovery or compensation mechanisms for functional improvement. Recovery refers to the restoration of motor function within an area of the motor cortex that was initially lost after injury. Compensation occurs when areas of the motor cortex adapt to take on motor functions lost after the injury. Rehabilitation training that forces or encourages using avoided movements can re-engage the neglected neural circuits within the motor cortex and reinstate these movement representations. This has been demonstrated in both animal models and human patients (Chandramouli et al., 2019).

5. THEORETICAL FRAMEWORKS ON REHABILITATION

5.1. Rehabilitation goals

Rehabilitation goals of children with CP emphasize maintaining and improving quality of life, maintaining achieved milestones, and preventing secondary complications. Independent of various rehabilitation approaches, children with CP would benefit from periods of intensive physiotherapy that enhances motor development especially during intense growth periods (Papavasiliou, 2009). Active participation and the highest possible level of independence during daily living activities, such as standing and walking, are primary goals of rehabilitation in children with CP (Becher, 2002). Gait rehabilitation methods, such as robot-assisted gait training (RAGT), are devoted to task-specific approaches accompanied by a high-repetition-rate of the gait cycle which was proved to enhance neuroplasticity and to improve the ambulatory potential (Meyer-Heim, 2013).

5.2. Robot-assisted gait training with Lokomat

In 1999, a group of engineers developed the very first automated gait training device named Lokomat (Hocoma AG, Switzerland). Since then, it was implemented in comprehensive gait rehabilitation programs of neurologic patients. Lokomat is designed as bilateral robotic orthoses to guide the patient's leg movements in a gait-like pattern with highly repeatable predefined hip- and knee-joint trajectories in the sagittal plane. Robotic orthoses equipped with foot lifters maintain passive ankle dorsiflexion in the stance and swing phases (Lünenburger et al., 2007). Computer-controlled motors, precisely synchronized with the speed of the treadmill, move the patient's legs through trajectories that mimic physiological gait patterns

(Colombo et al., 2000). The computer-controlled guidance allows individual adjustments of different gait parameters. Due to the body-weight support system (BWSS), body loading can be dosed progressively and adjusted to every patient individually (Riener et al., 2005). Patient's motor performance is enhanced by augmented feedback such as games which help to engage the patient's activity and keep them motivated. The game could respond to the patient's activity in the Lokomat and provide instant feedback to the child and the therapist (Ammann-Reiffer, 2017; Aurich-Schuler, 2017). Lokomat may strengthen neural pathways and enable the nervous system to explore movement variability associated with the production of coordinated locomotion. As practicing over-ground walking is often not possible in children with severe motor impairments, these patients require a simplified and safe therapeutic environment, such as provided by Lokomat, which in addition can provide prolonged training duration with many repetitions of steps, while inducing a reproducible, kinematically consistent, symmetrical gait pattern (Zwicker and Mayson, 2010; Kurz et al., 2011). In this sense, the Lokomat, the most used walking robotic aid for gait rehabilitation that can be performed safely and playfully to maintain a high level of motivation and treatment adherence especially in pediatrics.

5.2.1. Latest available research

RAGT seems promising in the functional improvements of gait and musculoskeletal structures (e.g. muscles and joints). The vast majority of studies dedicated to functional improvement of standing and walking (Meyer-Heim et al., 2009) concluded that RAGT effects on the gross motor were maintained up to 6-month follow-ups (Meyer-Heim and van Hedel, 2013). Beretta et al. (2020) observed increased walking endurance tested by the 6MWT in a retrospective analysis of 182 children

with CP and acquired brain injury. Schuler et al. (2011) reported that virtual realities used during RAGT seem to be efficient motivational tools to increase children's muscular effort in the pediatric Lokomat because the gaming aspect of virtual realities keeps children highly engaged during repetitive tasks. Furthermore, Aurich-Schuler (2017) reported that Lokomat induced such activation patterns of sEMG in rectus femoris and vastus medialis muscles that were highly similar to physiological over-ground walking. Vrečar et al. (2013) explored that a 4-week RAGT program can increase passive joint range of motion in lower extremities up to 10°. Finally, the recent study (Žarković et al., 2020) suggested that RAGT can improve SVMC of lower extremities in children with CP. Despite functional improvements that followed RAGT, only a few studies reported changes in spatiotemporal parameters, 3D kinematics, and kinetics. For example, Beretta et al. (2015) reported increased ROM of sagittal plane hip kinematics during the whole gait cycle that followed RAGT. Similarly, Druzbicki et al. (2013) reported a significant improvement in the maximal range of hip joint flexion kinematics. Wallard et al. (2012; 2014) highlighted a significant improvement in knee and ankle sagittal kinematics and dynamic balance control following RAGT combined with virtual reality in CP children who walk in jump gait pattern. Another study from Wallard et al. (2017) focused on the effect of RAGT on the dynamic equilibrium control during walking in CP children by analyzing different postural strategies. It seems that RAGT induces a more appropriate control of the upper body associated with an improvement of the lower limbs' kinematics.

6. METHODS

6.1. Study design

An empirical quantitative evaluation form of the research study using descriptive statistics to explain causalities and consequences among individual variables (Hendl, 2016). The research study was divided into four parts:

6.1.1. Preparation phase

The preparation phase aimed to continuously map and analyze available literature that captures the latest available scientific work on CP and RAGT. Literature research was supported by consultations with medical providers and biomechanics experts from the Czech Republic, Switzerland, and Slovenia to enrich the theoretical knowledge of the PI, and structure better the future study design. This was followed by multiple research fellowships in rehabilitation centers and hospitals in the Czech Republic; Switzerland; and Slovenia which included a gathering of practical experience on how to work with children with CP; operate the RAGT device; work in gait laboratory; and assist during data collection. The preparation phase successfully resulted in a definition of the aim of the research, hypotheses, methods, and selection of suitable medical facilities that would provide a supportive environment to conduct a research study. As in 2015 Czech republic lacked a medical facility that would embrace a gait laboratory, pediatric rehabilitation department, and RAGT in one place, an accredited medical facility was found in Slovenia. Therefore, this research study resulted in cooperation among two institutions Charles University, Faculty of sports and physical education, and University Rehabilitation Institute of Republic Slovenia - Soča.

Finally, a detailed study design was proposed to both institutions. The research study received ethics committee approvals from the Faculty of Sports and Physical education at Charles University, the Czech Republic (no.120/2015 dated August 12, 2015), and Slovenian National Ethics Committee, URIS (dated October 5, 2015). Both approvals are attached in the Appendix part (see Chapter 13). The study complied with ethical principles stated in the Declaration of Helsinki, Convention on Human Rights and Biomedicine, and International Ethical Guidelines for Health-related Research Involving Humans, and it completely excludes impairment of patients' interests and damage to health. The parents of the children were informed of the study procedures, risks, and benefits, and provided written informed consent before their children participating in the study.

6.1.2. Executive phase

The executive phase aimed to collect data according to the approved study design. The detailed description of data collection follows. The executive phase took place at the URIS in Ljubljana, Slovenia.

6.1.3. Analysis phase

This phase aimed to thoroughly analyze obtained data and find suitable descriptive statistics methods on how to evaluate and interpret results. Literature research on suitable statistics methods was further supported by consultations with biomechanics and kin-anthropology experts from the Faculty of Sports and Physical education at Charles University, and the Faculty of biomedical engineering, CTU. Finally, reliable and valid statistical methods that would analyze the research findings were chosen

based on literature research, characteristics of data, and recommendations of biomechanics experts from institutions mentioned above.

6.1.4. Interpretation phase

This phase followed the data analysis and aimed to explain causalities and consequences among variables. Finally, this phase summarized the most important research findings and limits of the research study.

6.1.5. Definition of roles and responsibilities

The Principal Investigator (PI), Dragana Žarković, was the primary individual responsible for the preparation and creation of the study design; searching for a facility that would provide a supportive environment for conducting the research study; establishing the cooperation among Faculty of physical education and sport and URIS; executing procedures needed for the data collection; providing the 4-week RAGT intervention program; data processing and analysis; selection of statistical methods and preparation of all the data for statistical evaluation; publication process and writing the scientific articles on the aforementioned topic of the research study. All individuals that anyhow contributed during the research study are mentioned in the relevant subchapter below.

6.2. Aim of the research study

The purpose of this research study was to investigate the effects of a 4-week RAGT intervention as monotherapy on the quality of gait patterns in spastic diparesis children with CP.

6.3. Scientific question and hypotheses

Can RAGT induce a more physiological gait in ambulatory children with CP that would be comparable with healthy children?		Method used to confirm/reject hypothesis
H0	The gait pattern of children with CP will remain unchanged following RAGT intervention.	All procedures
H1	RAGT will induce a more physiological sEMG muscle activity by the means of approximation to the normative curve.	CGA - sEMG
H2	RAGT will induce more physiological joint kinematics trajectories by the means of approximation to the normative curve.	CGA - joint kinematics
H3	RAGT will induce more physiological gait kinetics by the means of approximation to the normative curve.	CGA - kinetics
H4	RAGT will enhance the ability of children with CP to walk farther distances.	CGA - spatiotemporal parameters, 6MWT
H5	Children with CP will increase the PROM in all joints following RAGT intervention.	Clinical tests - PROM
H6	Children with CP will show a higher ability to perform selective movements of hip, knee, and ankle joint following RAGT intervention.	Clinical tests - SCALE

Table 1: Overview of scientific question and individual hypotheses.

6.4. Inclusion criteria of the research study

Inclusion criteria were: CP type spastic diparesis; Gross Motor Function Classification (GMFCS) I-III; ability to walk independently for at least short distances; femur length at least 21 cm; age 5–15 years; ability to communicate fear, pain, or discomfort; ability to follow simple instructions; no botulinum toxin in the last 3 months before RAGT; no orthopedic surgical intervention in the last 12 months; no anti-spastic medications; no severe contractures; and ability to attend 20 RAGT sessions scheduled in 20 consecutive weekdays (Meyer-Heim et al., 2009; Schuler et al., 2011; Meyer-Heim and van Hedel, 2013; Vrečar, 2013; Beretta et al., 2015; Wallard et al., 2017, Beretta et al., 2020).

6.5. Data collection

As this study aimed to explore effects followed by RAGT which include an extensive amount of variables, the data collection was divided into two parts:

- CGA in the gait laboratory
- reliable, valid, and standardized clinical evaluations

The combination of the CGA and clinical evaluations allows for a comprehensive interpretation of gait pathologies in children with CP. Methods were chosen based on the latest literature research and PI's own empirical experience. This research study used standardized, valid, and reliable methods that are routinely used in the assessment of children with CP. CGA (Wren et al., 2011), PROM (Nordmark et al., 2009), and 6MWT (Thompson et al., 2008) are the most frequently used in clinical decision-making, and monitoring outcomes following therapeutic or surgical interventions in children with CP. Additionally, this research study included the tool for SVMC assessment - SCALE (Fowler, 2009).

6.6. Procedures

All children with CP enrolled in the research study were treated as out-patients, and following procedures were covered by the Slovenian healthcare insurance system. All children with CP were evaluated in the same gait laboratory and same premises of the children's rehabilitation department at URIS. Data was collected by following standardized protocols for both clinical and gait analysis procedures. All procedures were performed in the exactly same order before and after completing the 4-week RAGT intervention. A detailed description of procedures and RAGT intervention follows.

6.6.1. Computerized gait analysis

The CGA was performed in the Kinesiology and Biomechanical Laboratory of URIS by the PI, two same physiotherapists, and two biomechanics experts. The CGA included 3D gait analysis consisting of joint kinematics, kinetics, sEMG, and spatiotemporal parameters.

Anthropometry

First, all children with CP were measured weight, height, leg length, knee and ankle joints circumferences (Baker, 2013). This data was further used by biomechanics experts for data processing.

Placement of sEMG electrodes

The skin of children with CP was gently abraded, and 3M Red Dot 2560 & 2570 Multi-purpose Monitoring Electrodes were placed on the following muscles bilaterally according to the SENIAM recommendations (Hermens et al., 2000): tibialis anterior (TA), medial gastrocnemius (MG), rectus femoris (RF), and biceps femoris (BF). A neutral reference electrode was attached to the tensor fascia latae muscle (Schuler et al., 2011). A multimeter was used to evaluate the values of skin resistance. Values between 0-10 Ohm were considered sufficient, whereas values over 10 Ohm were considered too high. If needed, the skin preparation procedure was repeated to assure proper skin resistance and electrode attachment (Hermens et al., 2000; Baker, 2013).

Placement of reflective markers

Subsequently, 17 reflective markers (Vicon, Oxford Metrics, Oxford, UK) were attached directly to the skin of children with CP. Markers were attached bilaterally to the following body areas concerning the Vicon Plug-in-Gait biomechanics model (Davis et al., 1991): second metatarsal joint; middle of the Achille´s tendon; malleolus lateralis; center of the tibia; lateral femoral epicondyle; lateral side of the thigh; spina iliaca anterior superior (SIAS); L5; Th10; sternum.

CGA data collection

Biomechanics experts calibrated the VICON camera system (0.3 MPix VICON, Oxford Metrics, Oxford, UK) before the data collection. All children with CP were told to walk barefoot in the pre-designed 10-meter flat-surface pathway to adapt to space. Subsequently, children with CP were supposed to stay still in the center of the AMTI force plates (AMTI OR6) in an anatomical position so that biomechanics experts could record the neutral position of all body segments. Afterward, children with CP were appealed to walk barefoot without walking aids at preferred speed and according to physical capacities for a minimum of ten trials on the same pre-designed 10-meter flat-surface pathway in the gait laboratory. Kinematics, kinetics, and sEMG data were collected and recorded simultaneously. 3D kinematic data was recorded by using a 6-camera VICON system (0.3 MPix VICON, Oxford Metrics, Oxford, UK) with a sampling frequency of 50 Hz until the course of three completed trials was obtained. Kinetics was recorded by using AMTI force plates (AMTI OR6, Advanced Mechanical Technology Inc., Watertown, MA) at 1 kHz sampling frequency. Muscle activity was recorded with an 8-channel sEMG sampling frequency at 1 kHz (Noraxon TeleMyo 2400T, Noraxon U.S.A. Inc.).

Figure 3: An 11-years-old girl with CP during CGA (source: own).

6.6.2. Clinical tests

All clinical tests were performed by the PI and senior pediatric physiotherapist from Children's rehabilitation department.

Passive joint range of motion

PROM is a routinely used assessment that informs about the passive range of motion of particular joints and the presence of contractures (Kilgour, 2003). The assessment was always performed by two same assessors (the PI and senior pediatric physiotherapist). One assessor measured the range of motion using a standardized plastic goniometer (McWhirk et al., 2006). Another assessor performed the passive movement and fixation of the child's lower limb. All children with CP were asked to relax assessed lower limb, and remain passive during the evaluation. The assessor passively moved lower limb joints into such a position until the maximum joint barrier occurred, and this value was recorded in the score sheet. A detailed description of the PROM procedure follows.

Hip joint extension

Children with CP were assessed in a supine position with fixed lumbar lordosis to keep the pelvis in a neutral position and to prevent an error during measurement. The untested leg was flexed whilst the tested leg was passively moved from maximal flexion to extension. Goniometer was attached to trochanter major to measure the angle between the trunk and the thigh. The physiological value is zero degrees. Values ranging between 0–20° mean that hip flexor contracture is present; values ranging between 0 to -15° mean that hip flexors are stretched (Katz, et al., 1992; Nordmark, 2009).

Hip joint rotations

Children with CP were assessed in a prone position with a fixed pelvis to prevent anteversion. The tested leg was passively moved to internal and subsequently external rotations. A goniometer was attached to the center of the patella to measure the angle between the knee and shin bone. The physiological value is 45° for each of the rotations (Katz, et al., 1992; Nordmark, 2009).

Knee joint extension

Children with CP were assessed in a supine position with fixed lumbar lordosis to keep the pelvis in a neutral position to prevent an error during measurement. The untested leg was flexed whilst the tested leg was passively moved from maximal knee flexion to extension. A goniometer was attached to the lateral epicondyle of the femur to measure the angle between the thigh and shin bone. The physiological value is 180°. Values ranging between 0–20° mean that hamstring contracture is present; values ranging between 0 to -10° or even more mean that knee hyperextension is present (Katz, et al., 1992; Nordmark, 2009).

Popliteal angles

Children with CP were assessed in a supine position to evaluate the hamstring contracture. Lumbar lordosis was fixed to keep the pelvis in a neutral position and to prevent an error during measurement. Both unilateral and bilateral popliteal angles were measured and the goniometer was attached to the lateral femoral epicondyle. Physiological values are 180° for bilateral and 130° for unilateral popliteal angles (Katz, et al., 1992; Berge et al., 2007).

Ankle joint dorsal flexion

Children with CP were assessed in a supine position. The measurement was performed with flexed and extended knee joint. In both measurements, the goniometer was attached to the medial malleolus to measure the angle between shinbone and foot. Physiological values range between 30–40° (Katz, et al.).

Selective Control Assessment of The Lower Extremity

SCALE test was used to assess the selectivity of movements in the hip, knee, ankle, subtalar joint and fingers. Detailed description of examined joints and positions is described below (Fowler et al., 2009; Fowler et al., 2010).

Hip joint

The hip joint was assessed in a side-lying position with the hip and knee fully extended. The tested limb was supported medially at the knee and ankle. For better stability, the untested limb was flexed. The tested motion is hip flexion while keeping the knee extended. Children with CP were asked to flex, extend then flex the hip while keeping the knee extended.

Knee joint

Children with CP were in a sitting position with the legs over the edge of the exam table. Children with CP were asked to extend, flex then extend the knee while keeping the hip flexed.

Ankle joint

Children with CP were in a sitting position with the legs over the edge of the exam table. The knee joint was extended and the assessor supported the calf. Children with CP were asked to dorsiflex, plantar flex then dorsiflex the ankle while maintaining knee extension.

Foot/subtalar Joint

Children with CP were in a sitting position with the legs over the edge of the exam table. The knee joint was extended and the assessor supported the calf. Children were asked to invert, evert then invert while maintaining knee extension.

Toes

Children with CP were in a sitting position with the legs over the edge of the exam table. The knee joint was extended and the assessor supported the heel. Children were asked to flex, extend then flex toes without moving ankle or knee.

Six-minute walk test

Timed 6MWT assessed the maximum walked distance in 6 minutes. This test was performed in a non-distracting environment of a 100-meter long corridor that was intended for walk tests at the rehabilitation department of URIS. All children with CP wore comfortable footwear as well as orthoses if regularly used. All children with CP were told to walk at a self-selected speed that they typically use for long walks and avoid talking. Running or faster walking was not allowed during the test. Both assessors were present and provided encouragement to keep children with CP engaged in the task for full 6 minutes (de Groot and Takken, 2011). The total distance walked was recorded.

6.6.3. Definition of limb impairment

SCALE and PROM evaluations defined the more and less affected lower limb. These were administered as "more impaired limb" (MIL) and "less impaired limb" (LIL). (Fowler et al., 2009; Syczewska and Świecicka, 2016).

6.7. Robot-assisted gait training intervention

The RAGT was performed by the PI under the supervision of the senior pediatric physiotherapist from Children's rehabilitation department.

Pre-intervention procedure

The RAGT device Lokomat Pro (Hocoma AG, Volketswil, Switzerland) was used in the therapy protocol (TP). All children with CP were measured upper and lower leg lengths before the RAGT intervention. Upper leg length is a distance between trochanter major and lateral femoral epicondyle. Lower leg length is a distance between lateral femoral epicondyle and floor. All children with CP wore shoes while taking measures of lower limbs. Values from measurements were transferred to the Lokomat Pro device computer, and the software automatically generated the recommended settings for robotic orthoses. Pediatric, as well as the adult model of robotic orthoses, were used during the TP. Afterward, the proper size of the trunk harness and cuffs for lower extremities were chosen for every child individually according to the recommendations of the manufacturer's Operator's manual.

Figure 4: Measurements of upper and lower leg lengths (source: Lokomat Pro Operator's Manual).

Figure 5: Lokomat Pro pediatric (left) and adult orthoses (right) (source: own).

Installation process

The installation process of children with CP took around 15 minutes and can be seen

in the kinogram below (see Figure 6).

Figure 6: Installation process of children with CP in the RAGT device (source: Žarković et al., 2019).

Intervention

TP consisted of twenty sessions scheduled for 20 consecutive workdays with a minimum duration of 30 and up to a maximum of 45 minutes (Vrečar et al., 2013; Wallard et al., 2017). Therapy duration was increased progressively by at least 3 minutes every other day. All children with CP walked with augmented feedback that comprised of a motivational video game (Schuler et al., 2011; Schuler et al. 2013; Wallard et al., 2017). The treadmill speed was synchronized with the movements of the robotic orthoses and set to a comfortable walking speed of every child individually. These parameters were set by following the child's ability to walk at a certain speed, follow the augmented feedback and maintain an upright posture. All children wore shoes during the TP. At the beginning of the RAGT program, all children had an initial level of BWS set to 50% of body weight (Schuler et al., 2013). The BWS was further decreased for every child individually until the knee started to collapse into flexion during the stance phase due to the increased load of body weight. All children walked with augmented biofeedback. For consistency, the PI was present at every RAGT session to follow the progression, encourage the child to walk actively, and keep an extended posture (see Figure 7).

Figure 7: A 5-year-old boy with spastic diparesis during RAGT using the Lokomat Pro (source: own).

6.8. Data evaluation

6.8.1. CGA data processing

The CGA data was processed by two biomechanics experts from Kinesiology and Biomechanical Laboratory at URIS that followed standardized guidelines for data processing. Raw CGA data obtained from overground gait was high-pass filtered by the VICON system (VICON Nexus 1.8.3.) to enable analog data sampling with 1 kHz, and subsequently filtered with a 4th order low-pass Butterworth filter with a cut off frequency of 20 Hz (Kadaba et al., 1989; Baker, 2013). The data was normalized and the Vicon Plug-in-Gait model was used to generate kinematic and kinetic data (Davis et al., 1991). Joint angles were calculated based on 3D coordinates of markers. Internal joint moments and power were calculated based on joint kinematics and ground reaction forces recorded using force plates (Kadaba et al., 1989; MacWilliams et al., 2003; Baker, 2013). Force plates measured ground reaction forces and center of pressure (COP) trajectory (Baker, 2013). VICON Nexus 1.8.3. and Polygon 3.5.1. softwares (VICON, Oxford Metrics, Oxford, UK) were used to define the gait cycles, spatiotemporal parameters, joint angles, internal joint moments, and power. sEMG data was processed by MyoResearch XP 1.07 Master Edition software (Noraxon Inc., Scottsdale/USA). Raw sEMG signals were high-pass filtered with a bi-directional zero-lag Butterworth at a cut-off frequency of 10 Hz, rectified, and smoothed with a time window of 100 ms to create the linear envelope. The sEMG data was normalized to the maximum EMG recorded during the gait cycle (Fung et al., 1989; Burden and Bartlett, 1999; Burden et al., 2003; Bojanic et al., 2011; Aurich-Schuler, 2017; Ricklin et al., 2018).

As subjects walked for a minimum of ten trials, gait cycles were identified in each trial. Heel strike and toe-off markers were set automatically by the software program and adjusted manually if necessary. The gait cycle starts and ends with a heel strike of the same lower extremity (Perry, 2010; Baker, 2013). Within the cycles, the mean value of these trials was calculated to obtain 1 gait cycle and separate gait phases. The gait cycle was represented by 51 evenly spaced samples (0–100% in 2% steps). As this study aimed to explore whether RAGT can induce physiological gait changes in lower limbs that will be comparable to the healthy children, a comparison of all CGA variables was made with normative data curves from typically developing children (Hof et al., 2005; Winter, 2009). Normative data are an integral part of VICON and Myoresearch softwares. Subsequently, detailed gait analysis reports were generated by the software for every child individually together with the detailed overview of all variables in the .csv format datasheets. Gait analysis report data sheets including all kinematics, kinetics, sEMG, and spatiotemporal variables were used for statistical evaluation.

6.8.2. Statistical evaluation of CGA data

The statistical evaluation of CGA data was done by the PI in cooperation with a biomechanics expert from the Faculty of biomedical engineering, CTU. Data were evaluated by a custom-written MatLab program (MatLab software processes, MatLab R2010b, Mathworks, Inc., Natick, MA, USA). The following variables from the gait analysis report data sheets were prepared for statistical evaluation (see Table 2).

Group of variables (units of measurement)	List of variables (MIL, LIL)
sEMG signals (V)	biceps femoris, rectus femoris, medial gastrocnemius, tibialis anterior
3D joint kinematics (degrees)	pelvis, hip, knee, ankle, thorax tilt
kinetics (N)	hip, knee and ankle joints power and moments ground reaction forces (GRF) center of mass (COM) center of pressure (COP)

Table 2: Overview of variables from gait analysis report; *Legend:* Computerized gait analysis (CGA); More impaired limb (MIL); Less impaired limb (LIL).

A 5-step statistical analysis was done as follows:

1) calculation of the deviation of CP signals from the normative values of healthy children for all CGA variables by using normalized cross-correlation (NCC)

2) verification of data normality distribution

3) comparison of condition pre- and post-RAGT intervention by using Wilcoxon sign rank test

4) calculation of effect sizes

5) calculation of dependencies among selected pairs of variables by using Spearman correlation

First, gait cycle phases were identified according to Perry (2010) as: 0-2% initial contact; 2-12% loading response; 12-31% midstance; 31-50% terminal stance; 50-62% pre-swing; 62-75% initial swing; 75-87% midswing; 87-100% terminal swing. Subsequently, the deviation of CP signals from the normative values of healthy children (Hof et al., 2005; Winter, 2009) was calculated by normalized cross-correlation (NCC) for every child with CP (Mahaki et al., 2017; Kaso, 2018), every CGA variable, and for all gait cycle phases. This calculation was performed for MIL/LIL separately, and pre- and post-RAGT intervention to obtain twelve values of NCC "pre-intervention" and "post-intervention". Finally, the median value of twelve CP children NCC was calculated and further statistically compared. NCC was calculated by using the formula below:

$$NCC = \frac{\sum_{i=0}^{n-1}[x(i) \cdot y(i)]}{\sqrt{\sum_{i=0}^{n-1} x^2(i) \cdot \sum_{i=0}^{n-1} y^2(i)}}$$

Figure 8: NCC formula (source: Cohen, 1988; Kaso, 2018).

where x(i) and y(i) are two given discrete-time real signals (sequences). CC is affected by the shape, scaling and shift of the curves. Regarding the shift, this method allows for consideration both shift between two signals and shift from 0. Consequently, identical signals with different shifts from 0 generate different results. The NCC, also known as cross-correlation coefficient ranges between -1 and 1, where 1 indicates identical signals and -1 indicates an inverted signal. NCC considers both shifts in periods between the two signals and the shift from 0 (Cohen, 1988; Mahaki et al., 2017; Kaso, 2018).

The NCC was followed by the statistical evaluation that aimed to compare the pre- and post-intervention conditions of all children with CP. The Shapiro-Wilk test was used to verify data normality (Cohen, 1988). As normal data distribution has been rejected at the 0.05 significance level, the non-parametric Wilcoxon sign rank test (Cohen, 1988) was used for further statistical calculation of each variable at the 0.05 significance level.

$$z = \frac{(W - n(n+1)/4)}{\sqrt{\dfrac{n(n+1)(2n+1) - tieadj}{24}}},$$

Figure 9: Wilcoxon sign rank test formula (source: Cohen, 1988).

Furthermore, the Wilcoxon sign rank test was completed with the calculation of effect sizes where large effect was 0.5, a medium effect was 0.3, and a small effect was 0.1 (Cohen, 1988, Fritz et al., 2012).

$$r = \frac{z}{\sqrt{N}}$$

Figure 10: Effect size formula for non-parametric data (Fritz et al., 2012).

Additionally, the aforementioned statistical evaluation of sEMG, kinematics, and kinetics variables using the NCC in a custom-written MatLab program is visualized in Figure 11.
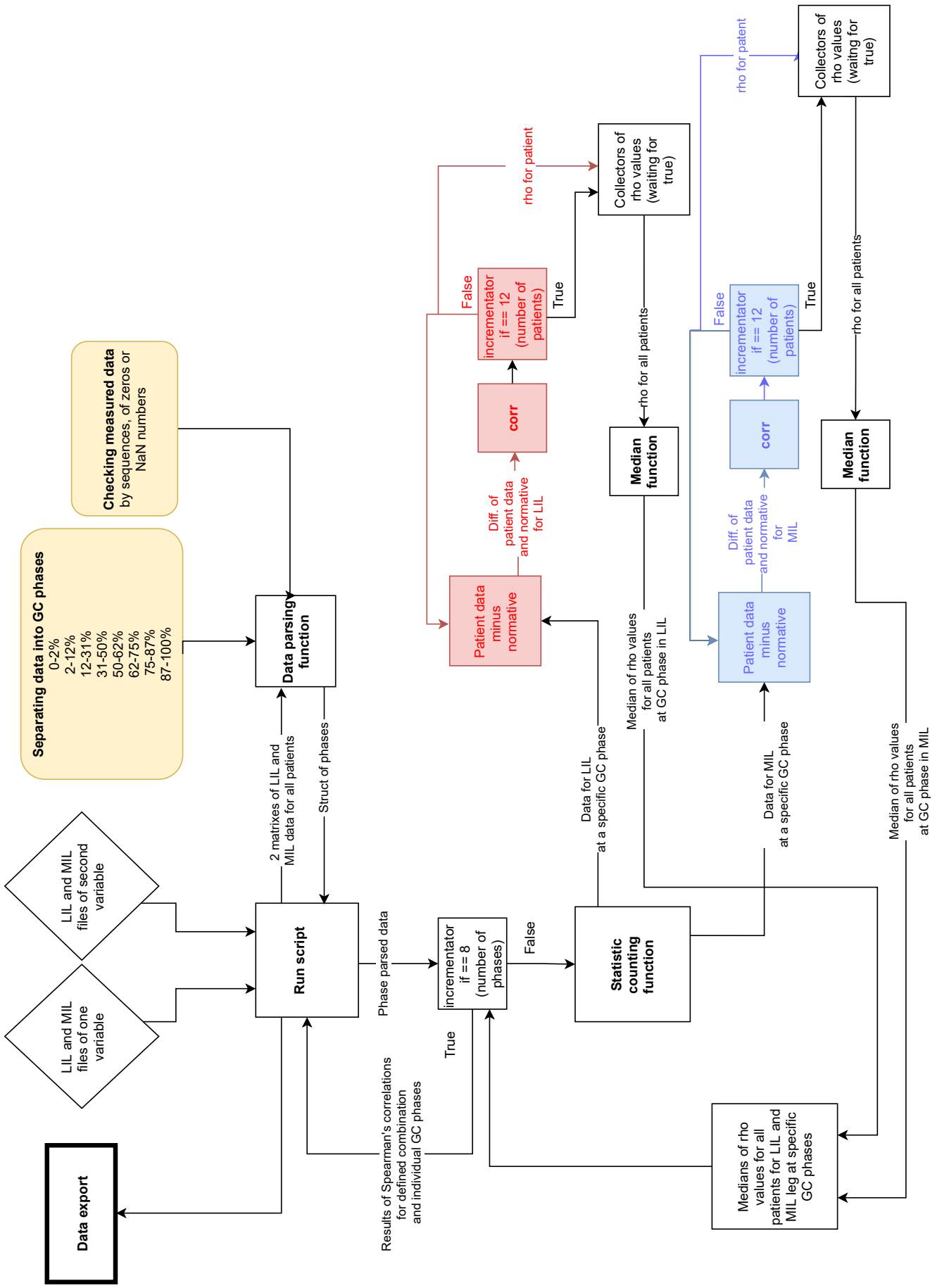
Figure 11: The principle of statistical evaluation of sEMG, kinematics and kinetics variables using the NCC in a custom-written MatLab program (source: own). *Legend:* More impaired limb (MIL); Less impaired limb (LIL); Gait cycle (GC); Not a number (NaN).

Finally, Spearman correlation was used to evaluate dependencies among selected pairs of variables (see Table 3 and Table 4).

Pairs of kinematics/kinetics variables (MIL, LIL)
pelvic tilt / knee flexion extension (°)
hip flexion extension / knee flexion extension (°)
knee flexion extension / ankle flexion extension (°)
hip rotation / knee abduction adduction (°)
hip abduction adduction / knee abduction adduction (°)
thorax tilt / pelvic tilt (°)

Table 3: Pairs of kinematics/kinetics variables; *Legend:* More impaired limb (MIL); Less impaired limb (LIL).

Pairs of sEMG variables for Spearman correlation (MIL, LIL)
RF / BF (V)
MG / TA (V)

Table 4: Pairs of sEMG variables; *Legend:* More impaired limb (MIL); Less impaired limb (LIL).

Spearman's rank correlation coefficient was used as normal data distribution has been rejected, A large correlation was 0.5, medium was 0.3 and small was 0.1 (Cohen, 1988).

$$r_S = 1 - \frac{6 \sum\limits_{i=1}^{n} d_i^{\,2}}{n^3 - n}$$

Figure 12: Spearman's rank correlation coefficient formula (source: Cohen, 1988).

Additionally, the aforementioned statistical evaluation of Spearman's rank correlation coefficient in a custom-written MatLab program is visualized in Figure 13.
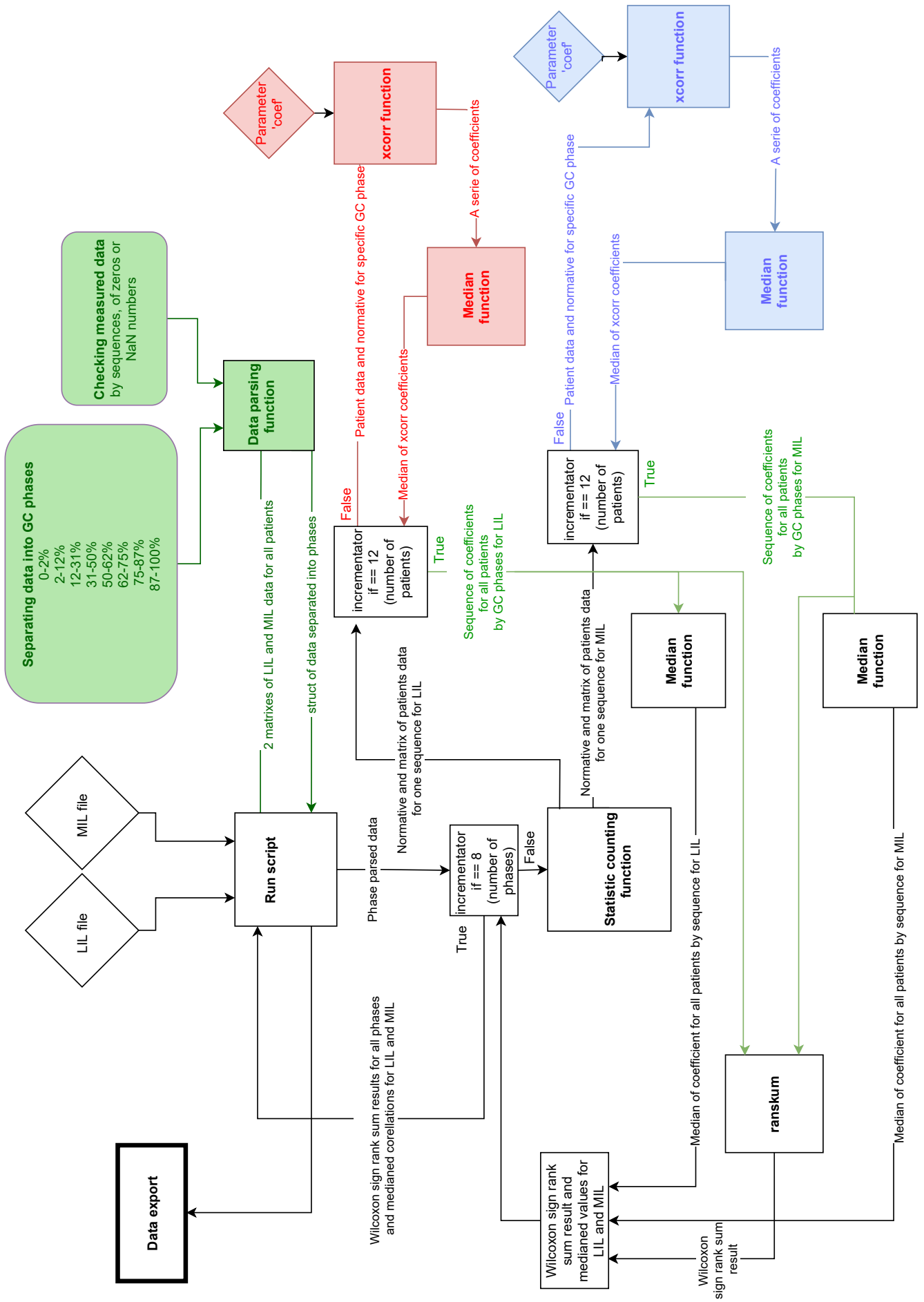
Figure 13: The principle of statistical evaluation of selected pairs of variables using Spearman's rank correlation coefficient in a custom-written MatLab program (source: own). *Legend: Legend:* More impaired limb (MIL); Less impaired limb (LIL); Gait cycle (GC); Not a number (NaN).

Additionally, the non-parametric Wilcoxon sign rank test was used to compare the pre- and post-intervention spatiotemporal variables (see Table 5) at the 0.05 significance level (Cohen, 1988).

Spatiotemporal parameters
cadence (steps/min)
double support (seconds)
foot off (%)
opposite foot contact (%)
opposite foot off (%)
single support (seconds)
step length (meters)
step time (seconds)
step width (meters)
stride length (meters)
stride time (second)
walking speed (meter/second)

Table 5: Spatiotemporal parameters.

6.8.3. Data processing of clinical tests

Clinical tests were processed by the PI. Pre- and post-RAGT intervention results of PROM angles, SCALE scores, and total distance walked in 6MWT were recorded in the score sheets and compared with normative values from typically developing children. Finally, the differences of 'pre-intervention and normative' and 'post-intervention and normative' conditions were calculated for every clinical test separately. The difference values of PROM, SCALE, and 6MWT tests were further statistically evaluated by using a custom-written MatLab program (MatLab software processes, MatLab R2010b, Mathworks, Inc., Natick, MA, USA).

6.8.4. Statistical evaluation of clinical tests

The statistical evaluation of clinical tests was done by the PI in cooperation with a biomechanics expert from the Faculty of biomedical engineering, CTU. A custom-written MatLab program (MatLab software processes, MatLab R2010b, Mathworks, Inc., Natick, MA, USA) was used. The following data sets for each of the MIL and LIL variables were prepared (see Table 6).

PROM (degrees) MIL, LIL	SCALE score MIL, LIL	6MWT
Hip joint extension	Hip joint	Total distance walked pre-RAGT intervention
Hip joint rotations	Knee joint	Total distance walked post-RAGT intervention
Knee joint extension	Ankle joint	
Popliteal angles	Foot/Subtalar joint	
Ankle joint dorsal flexion	Toes	

Table 6: Overview of clinical tests and variables; *Legend:* Passive range of motion (PROM); Selective Control Assessment of Lower Extremities (SCALE); Six-minute walk test (6MWT); More impaired limb (MIL); Less impaired limb (LIL).

The statistical evaluation was performed to compare the pre- and post-intervention patients' conditions. The Shapiro-Wilk test was used to verify data normality (Cohen, 1988). As normal data distribution has been rejected at the 0.05 significance level, the non-parametric Wilcoxon sign rank test (Cohen, 1988) was used for further statistical calculation of MIL and LIL separately (0.05 significance level).

$$z = \frac{(W - n(n+1)/4)}{\sqrt{\dfrac{n(n+1)(2n+1) - tieadj}{24}}},$$

Figure 14: Wilcoxon sign rank test formula (source: Cohen, 1988).

Furthermore, the non-parametric Wilcoxon sign rank test was completed with the calculation of effect sizes where large effect was 0.5, a medium effect was 0.3, and a small effect was 0.1 (Cohen, 1988, Fritz et al., 2012).

$$r = \frac{z}{\sqrt{N}}$$

Figure 15: Effect size formula for non-parametric data (Fritz et al., 2012).

7. RESULTS

7.1. Children with cerebral palsy

Twelve CP children with spastic diparesis (10.8±2.6 years old; 2 girls and 10 boys; GMFCS I-III) met all inclusion criteria and completed the RAGT program. The program was well-tolerated by all of the children and no adverse events were reported. The baseline data are summarized in Table 7.

Patient ID and gender	Age (years)	GMFCS level	Walking pattern	Lokomat orthoses
1F	11	II	Toe walking	A
2F	11	III	Crouch gait with dominantly spastic hip adductors	P
3F	15	III	Crouch gait	A
4M	5,5	III	Toe walking	P
5M	7	II	Toe walking	P
6M	8	III	Crouch gait	P
7M	9	I	Toe walking	P
8M	9	II	Toe walking	P
9M	10	II	Toe walking	P
10M	11	I	Toe walking	A
11M	12	II	Toe walking	A
12M	16	II	Toe walking	A

Table 7: Baseline data of children with CP. In total twelve children with CP (10.8±2.6 years old; 2 girls and 10 boys; GMFCS I-III) were enrolled. 9 children had toe walking pattern, 3 children walked in a crouch gait (Sutherland et al., 1993). *Legend:* M (male); F (female); GMFCS (Gross Motor Functional Classification Score); A (adult); P (pediatric).

7.2. Intervention

All children underwent 20 RAGT sessions. On average, the RAGT sessions were 39±6 minutes long, and the average walking speed was 1.4±2.38 km/h. The average distance walked during a single RAGT session was 969±172 meters with an average BWS of 14.8±4.76 kgs.

7.3. CGA results

Significant pre-post RAGT intervention differences (p<0.05) that indicate more physiological gait according to the normative data curves were found (Hof et al., 2005; Winter, 2009).

7.3.1. sEMG results

As this study enrolled CP children with spastic diparesis, the significant improvement was found mainly in bilaterally decreased muscle activity. BF and RF muscles decreased activity almost across all gait cycle phases. MG decreased activity mainly in terminal stance, midswing, and terminal swing phases. TA showed decreased activity almost in all phases except for terminal stance and midswing. In general, small to moderate effect sizes could be found in the sEMG analysis ranging between 0.40032-0.6245 (see Table 8). Table 8 summarizes sEMG quantitative changes including effect sizes for all children with CP. Examples of qualitative changes in sEMG activity together with normative data curves from typically developing children are shown in Figures 16-19.

BF/RF MIL agonist-antagonist pair showed a significant correlation in terms of their physiological muscle co-activation in the terminal stance, pre-swing, initial swing, and midswing phases. The only significant correlations in LIL were found in the midstance and terminal stance phases. MG/TA agonist-antagonist pair showed a significant correlation in terms of their physiological muscle co-activation in initial swing and midswing phases. In general, moderate to large correlations could be found in the sEMG agonist-antagonist pairs ranging between 0.503497-0.874126 (see Table 9). Table 9 summarizes sEMG agonist-antagonist pairs quantitative changes for all children with CP.

sEMG	Gait phase (p-value) / *Effect size*							
	IC	LR	MST	TS	PSW	ISW	MSW	TSW
BF MIL	0,007649	0,009633	0,00604	0,004742	0,00604	0,012063	0,009633	0,00604
ES	*0,544436*	*0,528423*	*0,560449*	*0,576461*	*0,560449*	*0,51241*	*0,528423*	*0,560449*
BF LIL	0,012792	0,020795	0,009633	0,004742	0,071189	0,002218	0,041389	0,004742
ES	*0,508168*	*0,47187*	*0,528423*	*0,576461*	*0,368295*	*0,6245*	*0,416333*	*0,576461*
RF MIL	0,003702	0,004742	0,002218	0,003702	0,002218	0,012063	0,00604	0,002873
ES	*0,592474*	*0,576461*	*0,6245*	*0,592474*	*0,6245*	*0,51241*	*0,560449*	*0,608487*
RF LIL	0,003346	0,002873	0,002873	0,002218	0,307821	0,03417	0,03417	0,012063
ES	*0,598912*	*0,608487*	*0,608487*	*0,6245*	*0,208167*	*0,432346*	*0,432346*	*0,51241*
MG MIL	0,022909	0,084379	0,03417	0,028056	0,03417	0,084379	0,018603	0,028056
ES	*0,464372*	*0,352282*	*0,432346*	*0,448359*	*0,432346*	*0,352282*	*0,480384*	*0,448359*
MG LIL	0,050461	0,075368	0,084379	0,041389	0,059739	0,009633	0,009633	0,04986
ES	*0,399275*	*0,362977*	*0,352282*	*0,416333*	*0,384308*	*0,528423*	*0,528423*	*0,40032*
TA MIL	0,022909	0,018603	0,084379	0,059739	0,03417	0,04986	0,157939	0,03417
ES	*0,464372*	*0,480384*	*0,352282*	*0,384308*	*0,432346*	*0,40032*	*0,288231*	*0,432346*
TA LIL	0,003346	0,002218	0,002873	0,002218	0,007649	0,007649	0,028056	0,009633
ES	*0,598912*	*0,6245*	*0,608487*	*0,6245*	*0,544436*	*0,544436*	*0,448359*	*0,528423*

Table 8: sEMG results. The deviation of CP signals from the sEMG normative values (Hof et al., 2005; Winter, 2009) of each variable was calculated by cross-correlation for every child's LIL and MIL separately pre- and post-intervention. Afterward, cross-correlation values 'pre-post intervention' were compared by using the Wilcoxon sign rank test. This table shows an overview of Wilcoxon sign rank test (p-value) results, including effect sizes for all variables across gait phases. Statistically significant results (p<0.05) are marked with yellow color. *Legend: ES* (effect size); More impaired limb (MIL); Less impaired limb (LIL); Initial contact (IC); Loading response

(LR); Midstance (MST); Terminal stance (TS); Pre-swing (PSW); Initial swing (ISW);

Midswing (MSW); Terminal swing (TSW); BF (biceps femoris); RF (rectus femoris);

TA (tibialis anterior); MG (medial gastrocnemius).

sEMG correlations	Gait phase (rho value)							
	IC	LR	MST	TS	PSW	ISW	MSW	TSW
BF/RF MIL	-0,02797	-0,11189	0,48951	0,65035	0,874126	0,811189	0,657343	0,314685
BF/RF LIL	0,335664	0,384615	0,783217	0,853147	0,384615	0,342657	0,377622	0,454545
MG/TA MIL	0,475524	0,524476	0,391608	0,20979	0,363636	0,72028	0,503497	0,370629
MG/TA LIL	0,251748	0,335664	0,307692	0,286713	0,377622	0,251748	0,629371	0,545455

Table 9: sEMG correlations results. Spearman correlation was used to evaluate

dependencies among agonist-antagonist pairs of muscles for every child's LIL and

MIL separately pre- and post-intervention. This table shows an overview of

Spearman correlation (rho-value) results. Statistically significant results (rho<0.5) are

marked with yellow color. *Legend:* More impaired limb (MIL); Less impaired limb

(LIL); Initial contact (IC); Loading response (LR); Midstance (MST); Terminal stance

(TS); Pre-swing (PSW); Initial swing (ISW); Midswing (MSW); Terminal swing (TSW);

BF (biceps femoris); RF (rectus femoris); TA (tibialis anterior); MG (medial

gastrocnemius).

EMG biceps femoris

Figure 16: Qualitative pre-post intervention changes in sEMG activity of biceps femoris. The interpretation is as follows: each of the muscles was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding EMG values expressed in Volts (V) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Biceps femoris decreased activity bilaterally and the curve of CP children tend to show a more physiological activation trend when compared to the normative curve. *Legend:* More impaired limb (MIL); Less impaired limb (LIL).
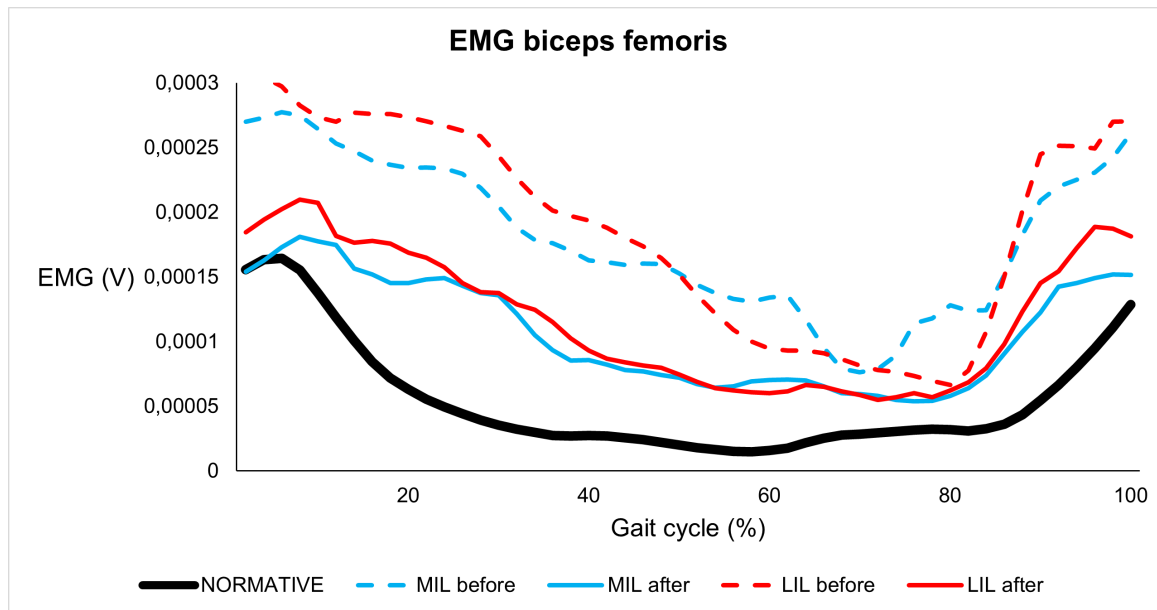
Figure 17: Qualitative pre-post intervention changes in sEMG activity of rectus femoris. The interpretation is as follows: each of the muscles was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding EMG values expressed in Volts (V) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Rectus femoris decreased activity bilaterally almost across all gait cycle phases, however, the trend of the non-physiological curve is still present. *Legend:* More impaired limb (MIL); Less impaired limb (LIL).

EMG tibialis anterior

Figure 18: Qualitative pre-post intervention changes in sEMG activity of tibialis anterior. The interpretation is as follows: each of the muscles was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding EMG values expressed in Volts (V) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Although tibialis anterior showed decreased activity almost in all phases except for terminal stance and mid-swing, the curve of CP children tends to show a more physiological activation trend when compared to the normative curve. *Legend:* More impaired limb (MIL); Less impaired limb (LIL).
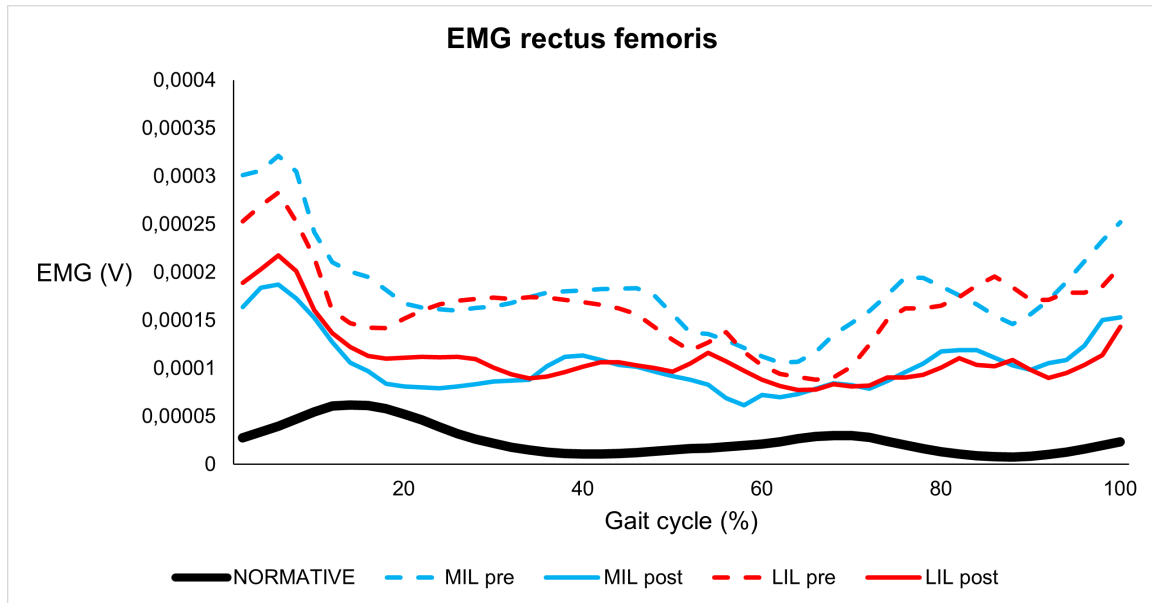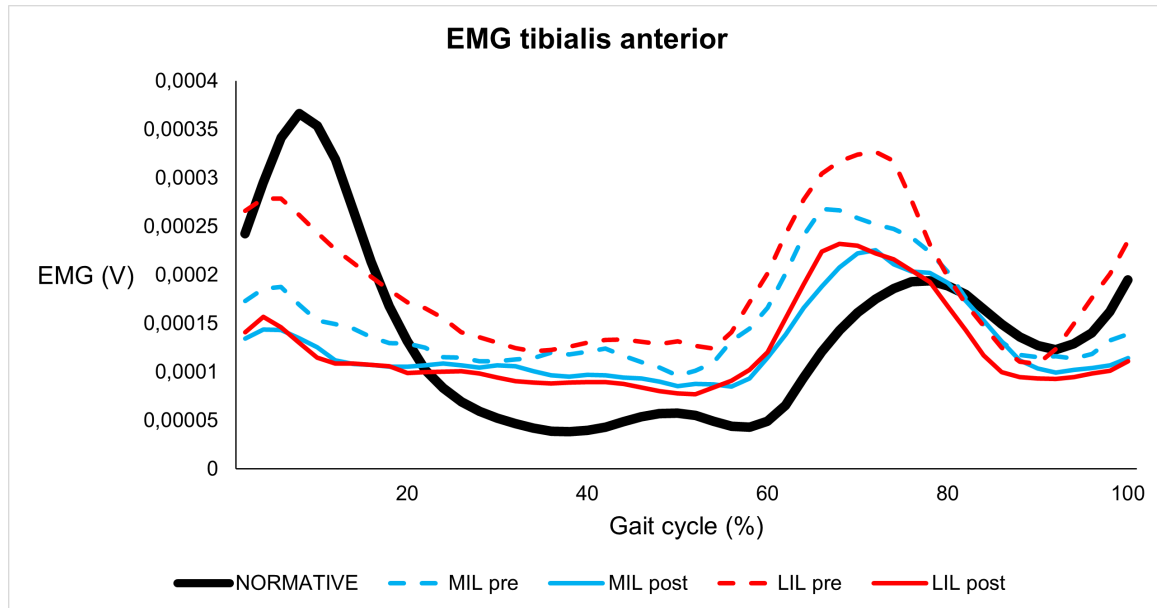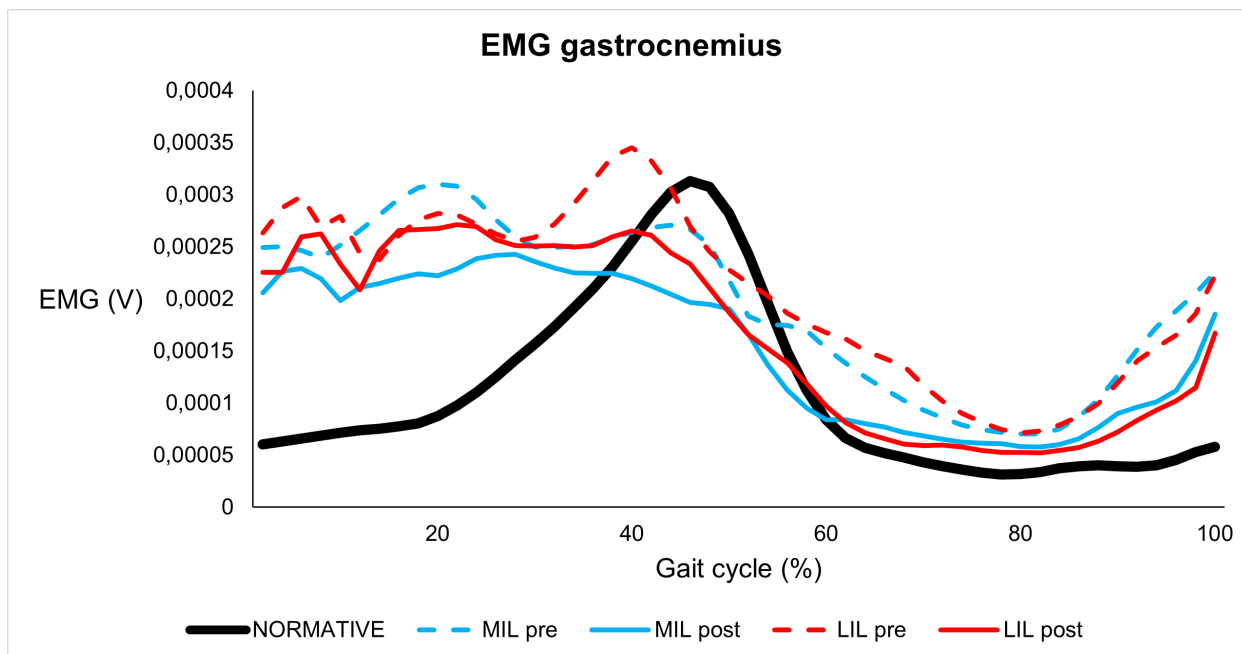
EMG gastrocnemius

Figure 19: Qualitative pre-post intervention changes in sEMG activity of medial gastrocnemius. The interpretation is as follows: each of the muscles was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases expressed in percents (axis x); and corresponding EMG values expressed in Volts (V) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Medial gastrocnemius decreased activity mainly in terminal stance, mid-swing and terminal swing phases, the curve of CP children tends to show a more physiological activation trend when compared to the normative curve. *Legend:* More impaired limb (MIL); Less impaired limb (LIL).

7.3.2. Joint kinematics results

The most significant bilateral kinematic changes were observed in hip rotations, foot progress, and thorax tilt followed by small to moderate effect sizes ranging between -0,41633 to -0.6245 (see Table 10). Internal hip rotation decreased almost across all phases. Foot progress angles showed a decreased trend of in-toeing almost across all phases. A decrease of anterior thorax tilt was observed bilaterally, however it was more accented on the less impaired side of the trunk. Table 10 summarizes joint kinematics quantitative changes including effect sizes for all children with CP. Examples of qualitative changes in joint kinematics activity together with normative data curves from typically developing children are shown in Figures 20-23. In general, moderate to large correlations ranging between -0.6 to 0.8286 were found. Table 11 summarizes joint kinematics pairs quantitative changes for all children with CP. Significant correlations in joint kinematics pairs in terms of their physiological range of motion were found bilaterally in pelvic tilt/knee flexion extension in pre-swing phase; knee flexion extension/ankle flexion extension in mid stance and initial swing phases; hip rotation/knee abduction adduction in midswing phase; and finally in thorax tilt/pelvic tilt across phases terminal swing up to initial swing.

Kinematics	Gait phase (p-value) / Effect size							
	IC	LR	MST	TS	PSW	ISW	MSW	TSW
Pelvic tilt MIL	0,346522	0,388186	0,58292	0,432768	0,388186	0,307821	0,307821	0,307821
ES	*0,192154*	*0,176141*	*0,11209*	*0,160128*	*0,176141*	*0,208167*	*0,208167*	*0,208167*
Pelvic tilt LIL	0,346522	0,346522	0,346522	0,307821	0,388186	0,530285	0,480177	0,346522
ES	*0,192154*	*0,192154*	*0,192154*	*0,208167*	*0,176141*	*0,128103*	*0,144115*	*0,192154*
Pelvic obliquity MIL	1	0,937473	0,307821	0,084379	0,028056	0,209427	0,813945	0,813945
ES	*0*	*0,016013*	*0,208167*	*0,352282*	*-0,44836*	*-0,25621*	*-0,04804*	*-0,04804*
Pelvic obliquity LIL	0,03417	0,116664	0,346522	0,937473	0,753684	0,388186	0,084379	0,03417
ES	*0,432346*	*-0,32026*	*-0,19215*	*0,016013*	*0,064051*	*0,176141*	*0,352282*	*0,432346*
Pelvic rotation MIL	0,63787	0,694887	0,272095	0,099481	0,157939	0,480177	0,813945	0,875329
ES	*-0,09608*	*-0,08006*	*-0,22418*	*0,336269*	*0,288231*	*0,144115*	*0,048038*	*0,032026*
Pelvic rotation LIL	0,071189	0,157939	0,346522	0,63787	0,937473	0,58292	0,239317	0,209427
ES	*0,368295*	*0,288231*	*0,192154*	*-0,09608*	*-0,01601*	*-0,11209*	*-0,24019*	*-0,25621*
Hip flexion/extension MIL	0,813945	0,813945	0,530285	0,63787	0,307821	0,157939	0,209427	0,432768
ES	*0,048038*	*0,048038*	*0,128103*	*0,096077*	*-0,20817*	*0,288231*	*0,256205*	*0,160128*
Hip flexion/extension LIL	0,272095	0,209427	0,099481	0,028056	0,239317	0,071189	0,071189	0,157939
ES	*0,224179*	*0,256205*	*0,336269*	*0,448359*	*-0,24019*	*0,368295*	*0,368295*	*0,288231*
Hip abduction/adduction MIL	0,136097	0,239317	0,099481	0,272095	0,157939	0,209427	0,272095	0,239317
ES	*-0,30424*	*0,240192*	*0,336269*	*0,224179*	*-0,28823*	*-0,25621*	*-0,22418*	*-0,24019*
Hip abduction/adduction LIL	0,157939	0,157939	0,480177	0,58292	0,694887	0,875329	0,875329	0,346522
ES	*0,288231*	*-0,28823*	*-0,14412*	*-0,11209*	*-0,08006*	*-0,03203*	*-0,03203*	*0,192154*
Hip rotation MIL	0,004742	0,003702	0,002218	0,002218	0,002218	0,002218	0,003702	0,00604
ES	*-0,57646*	*-0,59247*	*-0,6245*	*-0,6245*	*-0,6245*	*-0,6245*	*0,592474*	*0,560449*
Hip rotation LIL	0,157939	0,116664	0,04986	0,022909	0,041389	0,022909	0,022909	0,028056
ES	*-0,28823*	*-0,32026*	*-0,40032*	*-0,46437*	*-0,41633*	*-0,46437*	*0,464372*	*0,448359*
Knee flexion/extension MIL	0,432768	0,753684	0,346522	0,182338	0,58292	0,059739	0,239317	0,239317
ES	*-0,16013*	*-0,06405*	*-0,19215*	*-0,27222*	*-0,11209*	*-0,38431*	*-0,24019*	*-0,24019*
Knee flexion/extension LIL	0,694887	0,694887	0,694887	0,388186	0,694887	0,875329	0,813945	0,937473
ES	*0,080064*	*0,080064*	*0,080064*	*0,176141*	*0,080064*	*0,032026*	*-0,04804*	*-0,01601*
Knee abduction/adduction MIL	0,03417	0,03417	0,04986	0,099481	0,03417	0,018603	0,022909	0,018603
ES	*0,432346*	*0,432346*	*0,40032*	*0,336269*	*0,432346*	*-0,48038*	*0,464372*	*0,480384*
Knee abduction/adduction LIL	0,272095	0,272095	0,182338	0,63787	0,209427	0,059739	0,099481	0,03417
ES	*0,224179*	*0,224179*	*0,272218*	*0,096077*	*0,256205*	*-0,38431*	*0,336269*	*0,432346*
Ankle plantar/dorsal flexion MIL	0,239317	0,307821	0,480177	1	0,813945	0,157939	0,157939	0,875329
ES	*0,240192*	*0,208167*	*0,144115*	*0*	*-0,04804*	*0,288231*	*0,288231*	*0,032026*
Ankle plantar/dorsal flexion LIL	0,58292	0,480177	0,937473	0,346522	0,346522	0,530285	0,272095	0,63787
ES	*0,11209*	*0,144115*	*-0,01601*	*-0,19215*	*-0,19215*	*0,128103*	*0,224179*	*0,096077*
Foot tilt MIL	0,286003	0,373945	0,432768	0,753684	0,480177	0,813945	0,239317	0,209427
ES	*-0,21779*	*-0,18149*	*-0,16013*	*0,064051*	*0,144115*	*-0,04804*	*-0,24019*	*-0,25621*
Foot tilt LIL	0,116664	0,084379	0,059739	0,136097	0,432768	0,432768	0,813945	0,272095
ES	*0,320256*	*0,352282*	*0,384308*	*0,304243*	*0,160128*	*0,160128*	*0,048038*	*0,224179*
Foot progress MIL	0,012792	0,016369	0,00604	0,004742	0,015022	0,012063	0,028056	0,04986
ES	*-0,50817*	*-0,49002*	*-0,56045*	*-0,57646*	*-0,4964*	*-0,51241*	*-0,44836*	*-0,40032*
Foot progress LIL	0,00604	0,007649	0,022909	0,002873	0,002218	0,059739	0,116664	0,03417
ES	*-0,56045*	*-0,54444*	*-0,46437*	*-0,60849*	*-0,6245*	*-0,38431*	*-0,32026*	*-0,43235*
Thorax tilt MIS*	0,050461	0,050461	0,050461	0,022909	0,018603	0,018603	0,041389	0,03417
ES	*0,399275*	*0,399275*	*-0,39928*	*0,464372*	*-0,48038*	*-0,48038*	*-0,41633*	*-0,43235*
Thorax tilt LIS*	0,028056	0,028056	0,03417	0,03417	0,03417	0,028056	0,022909	0,028056
ES	*0,448359*	*0,448359*	*-0,43235*	*0,432346*	*-0,43235*	*-0,44836*	*-0,46437*	*-0,44836*

Table 10: Joint kinematics results. The deviation of CP signals from the normative kinematics values (Hof et al., 2005; Winter, 2009) of each variable was calculated by cross-correlation for every child's LIL and MIL separately pre- and post-intervention. Afterward, cross-correlation values 'pre-post intervention' were compared by using the Wilcoxon sign rank test. This table shows an overview of Wilcoxon sign rank test (p-value) results, including effect sizes for all variables across gait phases. Statistically significant results (p<0.05) are marked with yellow color. *Legend: ES* (effect size); More impaired limb (MIL); Less impaired limb (LIL); More impaired side (MIS); Less impaired side (LIS).
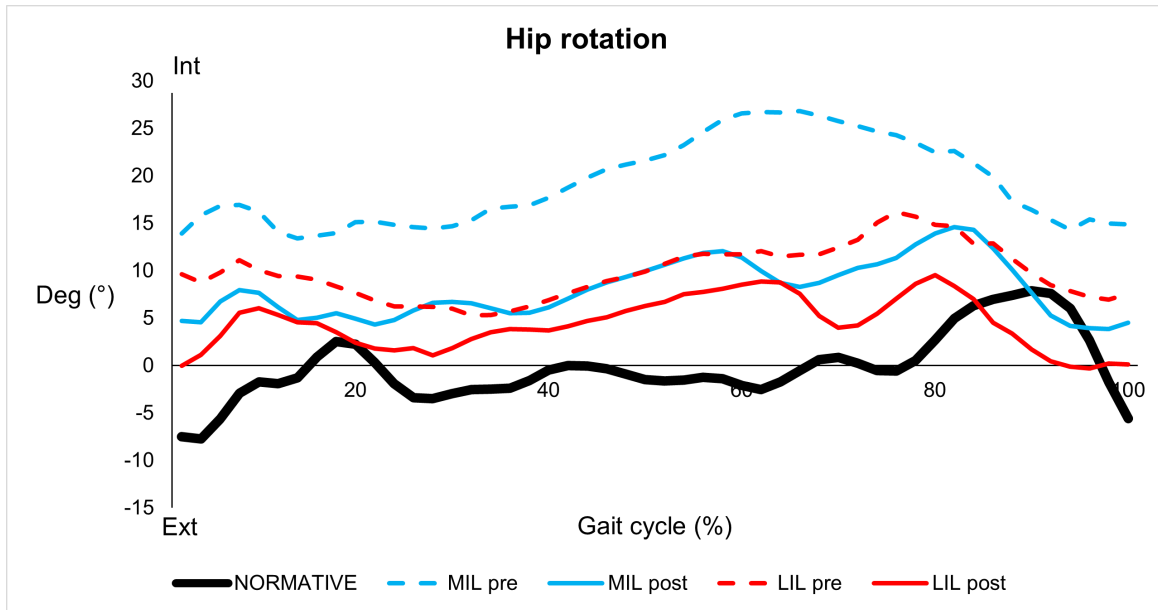
Figure 20: Qualitative pre-post intervention changes in hip rotations. The interpretation is as follows: each of the variables was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding joint range of motion values expressed in degrees (°) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Internal hip rotation decreased bilaterally almost across all gait cycle phases and the curve of CP children tend to show more physiological activation trend when compared to the normative curve. *Legend:* More impaired limb (MIL); Less impaired limb (LIL); Less impaired side (LIS); degree (Deg).
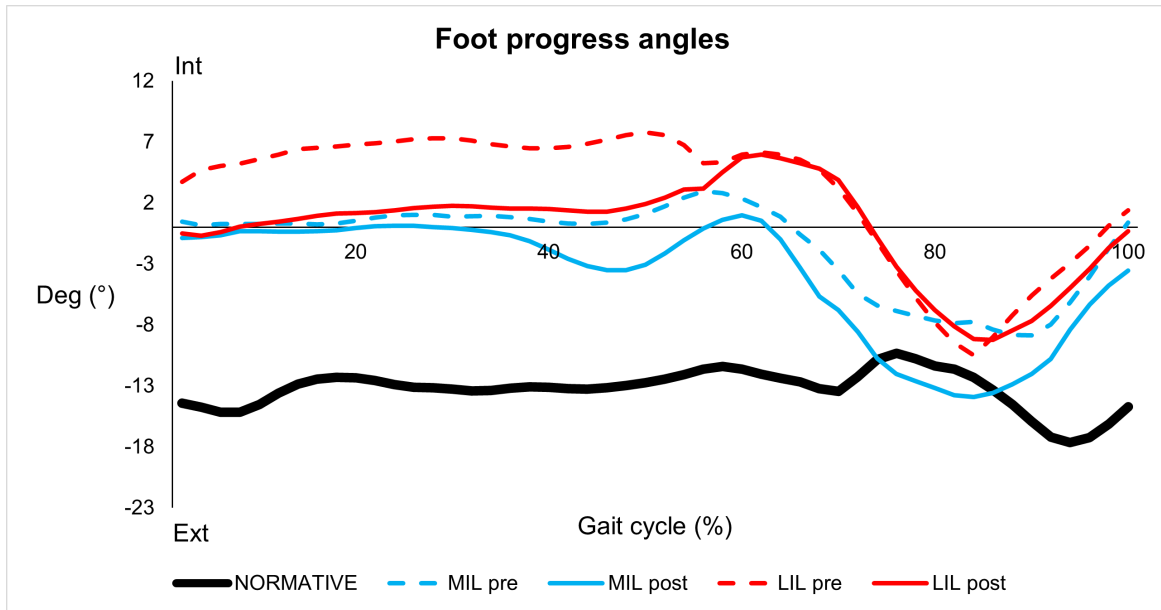
Figure 21: Qualitative pre-post intervention changes in foot progress angle. The interpretation is as follows: each of the variables was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding joint range of motion values expressed in degrees (°) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Although in-toeing significantly decreased almost across all phases, the trend of the non-physiological curve is still present. *Legend:* More impaired limb (MIL); Less impaired limb (LIL); Less impaired side (LIS); degree (Deg).
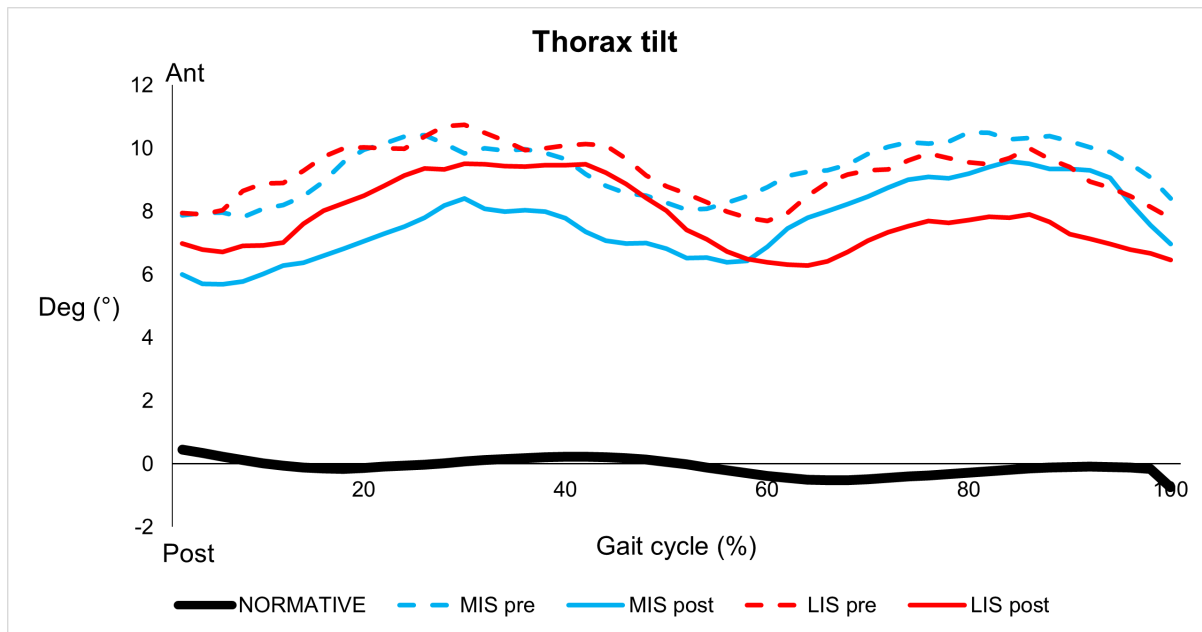
Figure 22: Qualitative pre-post intervention changes in thorax tilt. The interpretation is as follows: each of the variables was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding joint range of motion values expressed in degrees (°) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Anterior thorax tilt showed bilateral decreasing that was even more accented on the LIS of the trunk, however, the trend of the non-physiological curve is still present. *Legend:* More impaired limb (MIL); Less impaired limb (LIL); Less impaired side (LIS); degree (Deg).
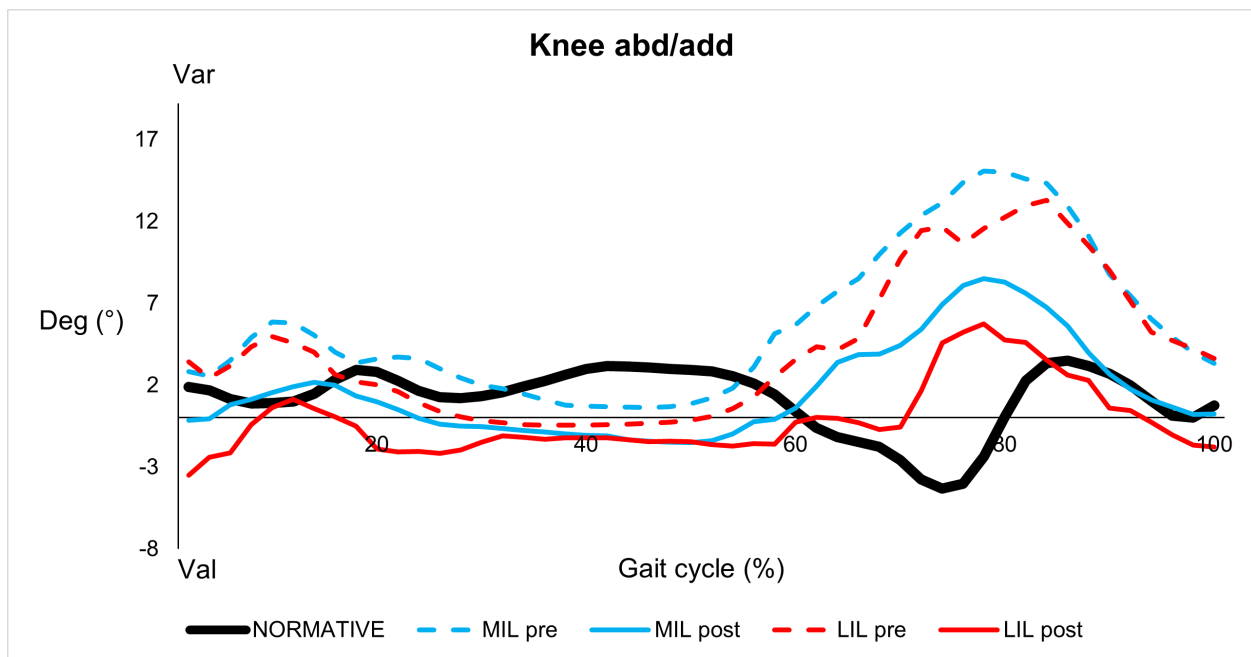
Knee abd/add

Figure 23: Qualitative pre-post intervention changes in knee abduction-adduction. The interpretation is as follows: each of the variables was divided into MIL and LIL pre-post intervention condition that was further compared with normative data curves (Hof et al., 2005; Winter, 2009) from typically developing children ('normative'). Changes are shown through the gait cycle phases and expressed in percents (axis x); and corresponding joint range of motion values expressed in degrees (°) (axis y). Black curve expresses normative data curves ('normative'); dotted blue curve expresses MIL pre-intervention ('MIL pre'); blue curve expresses MIL post-intervention ('MIL post'); dotted red curve expresses LIL pre-intervention ('LIL pre'); red curve expresses LIL post-intervention ('LIL post'). Although knee abduction-adduction decreased mainly in swing phases, the trend of the non-physiological curve is still present. *Legend:* More impaired limb (MIL); Less impaired limb (LIL); degree (Deg).

Kinematics/kinetics correlations	Gait phase (rho value)							
	IC	LR	MST	TS	PSW	ISW	MSW	TSW
Pelvic tilt/Knee flexion extension MIL	-0,02797	0	-0,3455	-0,3939	-0,7	0,0857	0,2381	-0,4857
Pelvic tilt/Knee flexion extension LIL	0,335664	-0,7	-0,6606	-0,8909	0,6	-0,0286	0,2381	0,3714
Hip flexion extension/Knee flexion extension MIL	0,475524	-0,3	-0,3212	-0,6667	0,4	0,0286	0,0952	0,4286
Hip flexion extension/Knee flexion extension LIL	0,251748	-0,2	0,4424	0,3455	-0,9	-0,6	0,381	0,2
Knee flexion extension/Ankle flexion extension MIL	0,116664	0	0,7818	-0,4788	-0,1	0,5429	-0,1905	0,2571
Knee flexion extension/Ankle flexion extension LIL	0,454545	-0,7	0,8182	-0,4424	-0,3	0,7143	-0,381	0,4286
Hip rotation/Knee abduction adduction MIL	0,475524	-0,1	0,503	0,0909	0,2	-0,2	0,6667	-0,0286
Hip rotation/Knee abduction adduction LIL	0,342657	-0,1	0,0424	-0,0667	-0,1	-0,2	0,7857	-0,1429
Hip abduction adduction/Knee abduction adduction MIL	-0,02797	0,9	-0,0788	0,3212	-0,6	-0,2571	-0,4524	0,6571
Hip abduction adduction/Knee abduction adduction LIL	-0,2571	-0,3	-0,2485	-0,3091	0,3	0,1429	-0,6905	0,2571
Thorax tilt//Pelvic tilt MIL	0,0857	-0,3	0,3455	0,5636	0,9	0,8286	-0,22143	0,7714
Thorax tilt//Pelvic tilt LIL	0,0286	0,1	0,3333	0,7333	-0,6	0,6	0,6905	0,3143

Table 11: Joint kinematics/kinetics correlations results. Spearman correlation was used to evaluate dependencies among kinematic variables for every child's LIL and MIL separately pre- and post-intervention. This table shows an overview of Spearman correlation (rho-value) results. Statistically significant results (rho<0.5) are marked with yellow color. *Legend:* More impaired limb (MIL); Less impaired limb (LIL); Initial contact (IC); Loading response (LR); Midstance (MST); Terminal stance (TS); Pre-swing (PSW); Initial swing (ISW); Midswing (MSW); Terminal swing (TSW).

7.3.3. Kinetics results

Kinetics showed a very few significant changes that were observed unilaterally and in a single gait phase only. These findings are further supported by small effect sizes ranging between -0,528342 to 0,41633 (see Table 12). Table 12 summarizes kinetics quantitative changes including effect sizes for all children with CP.

Kinetics	Gait phase (p-value) / Effect size							
	IC	LR	MST	TS	PSW	ISW	MSW	TSW
Hip flexion/extension moment MIL	0,480177	0,022909	0,084379	0,530285	0,63787	0,346522	0,157939	0,789675
ES	*-0,14412*	*-0,46437*	*-0,35228*	*-0,1281*	*0,096077*	*0,192154*	*-0,28823*	*-0,05445*
Hip flexion/extension moment LIL	0,346522	0,136097	0,813945	0,875329	0,432768	0,63787	0,018603	0,929153
ES	*0,192154*	*-0,30424*	*0,048038*	*0,032026*	*-0,16013*	*-0,09608*	*0,480384*	*0,018149*
Hip abduction/adduction moment MIL	0,272095	0,388186	0,937473	0,813945	1	1	0,694887	0,722108
ES	*0,224179*	*-0,17614*	*-0,01601*	*-0,04804*	*0*	*0*	*-0,08006*	*-0,0726*
Hip abduction/adduction moment LIL	0,182338	0,480177	0,63787	0,63787	0,58292	0,753684	0,307821	1
ES	*0,272218*	*-0,14412*	*-0,09608*	*-0,09608*	*0,11209*	*-0,06405*	*-0,20817*	*0*
Hip power MIL	0,937473	0,432768	0,694887	0,694887	0,260393	0,284503	0,937473	0,071189
ES	*-0,01601*	*0,160128*	*-0,08006*	*0,080064*	*0,229734*	*0,218466*	*0,016013*	*0,368295*
Hip power LIL	0,059739	0,247746	0,136097	0,239317	0,130665	0,575062	0,656642	0,209427
ES	*0,384308*	*0,235935*	*0,304243*	*-0,24019*	*-0,30853*	*-0,11443*	*0,090744*	*0,256205*
Knee flexion/extension moment MIL	0,012063	0,388186	0,307821	0,084379	0,58292	0,63787	0,813945	0,084379
ES	*-0,51241*	*-0,17614*	*-0,20817*	*0,352282*	*-0,11209*	*-0,09608*	*0,048038*	*-0,35228*
Knee flexion/extension moment LIL	0,157939	0,009633	0,059739	0,116664	0,209427	0,307821	0,63787	0,694887
ES	*-0,28823*	*-0,52842*	*-0,38431*	*0,320256*	*-0,25621*	*-0,20817*	*0,096077*	*-0,08006*
Knee valgus/varus moment MIL	0,753684	0,307821	0,059739	0,753684	0,530285	0,041389	0,530285	0,239317
ES	*0,064051*	*-0,20817*	*-0,38431*	*0,064051*	*-0,1281*	*0,416333*	*0,128103*	*0,240192*
Knee valgus/varus moment LIL	0,071189	0,937473	0,875329	0,875329	0,346522	0,480177	0,099481	0,272095
ES	*-0,3683*	*-0,01601*	*-0,03203*	*0,032026*	*0,192154*	*-0,14412*	*-0,33627*	*-0,22418*
Knee power MIL	0,432768	0,480177	0,753684	0,480177	0,51467	0,284503	0,813945	0,209427
ES	*-0,16013*	*0,144115*	*0,064051*	*-0,14412*	*-0,133*	*-0,21847*	*0,048038*	*0,256205*
Knee power LIL	0,937473	0,789675	0,480177	0,157939	0,15486	0,074462	0,929153	0,480177
ES	*-0,01601*	*-0,05445*	*-0,14412*	*-0,28823*	*0,290382*	*0,36411*	*0,018149*	*-0,14412*
Ankle flexion/extension moment MIL	0,694887	0,813945	0,530285	0,307821	0,432768	0,182338	0,307821	0,157939
ES	*-0,08006*	*0,048038*	*-0,1281*	*-0,20817*	*0,160128*	*0,272218*	*-0,20817*	*-0,28823*
Ankle flexion/extension moment LIL	0,63787	0,182338	0,937473	0,209427	0,875329	0,58292	0,63787	0,346522
ES	*0,096077*	*0,272218*	*-0,01601*	*-0,25621*	*0,032026*	*0,11209*	*0,096077*	*-0,19215*
Ankle power MIL	0,753684	0,041389	0,530285	0,388186	0,858955	0,507624	0,480177	0,63787
ES	*-0,06405*	*-0,41633*	*-0,1281*	*-0,17614*	*-0,03627*	*-0,13524*	*-0,14412*	*-0,09608*
Ankle power LIL	0,272095	0,929153	0,530285	0,694887	0,020795	0,444587	0,476907	0,813945
ES	*0,224179*	*-0,01815*	*0,128103*	*-0,08006*	*-0,47187*	*0,156047*	*-0,14519*	*0,048038*
GRF X MIL	0,656642	0,130665	0,432768	0,136097	0,161429			
ES	*-0,09074*	*-0,30853*	*-0,16013*	*-0,30424*	*-0,28583*			
GRF X LIL	1	0,109511	0,157939	0,239317	0,209427			
ES	*0*	*-0,32668*	*-0,28823*	*-0,24019*	*-0,25621*			
GRF Y MIL	0,423596	0,423596	0,239317	0,272095	0,400814			
ES	*-0,16334*	*-0,16334*	*0,240192*	*0,224179*	*0,171499*			
GRF Y LIL	0,858863	0,476907	0,753684	0,480177	0,875329			
ES	*-0,0363*	*0,145191*	*0,064051*	*-0,14412*	*-0,03203*			
GRF Z MIL	0,480177	0,530285	0,937473	0,530285	0,575403			
ES	*0,144115*	*0,128103*	*-0,01601*	*0,128103*	*0,114332*			
GRF Z LIL	0,789675	0,247746	0,388186	0,937473	0,015022			
ES	*0,054447*	*0,235935*	*0,176141*	*-0,01601*	*-0,4964*			
COM MIL	0,789675	0,929153	0,239317	0,63787	0,875329	0,875329	0,346522	0,239317
ES	*0,054447*	*0,018149*	*0,240192*	*0,096077*	*0,032026*	*-0,03203*	*0,192154*	*-0,24019*
COM LIL	0,432768	0,480177	0,694887	0,753684	1	0,937473	0,136097	0,480177
ES	*0,160128*	*0,144115*	*0,080064*	*0,064051*	*0*	*0,016013*	*0,304243*	*-0,14412*
COP X MIL	0,530285	0,875329	1	0,239317	0,865772			
ES	*0,128103*	*-0,03203*	*0*	*-0,24019*	*-0,0345*			
COP X LIL	0,858863	0,878482	0,813945	0,937473	0,888638			
ES	*0,036298*	*0,031209*	*0,048038*	*0,016013*	*-0,02858*			
COP Y MIL	0,116664	0,059739	0,136097	0,272095	0,236724			
ES	*-0,32026*	*-0,38431*	*-0,30424*	*-0,22418*	*-0,24152*			
COP Y LIL	0,373945	0,575062	0,136097	0,272095	0,207578			
ES	*0,181489*	*-0,11443*	*-0,30424*	*-0,22418*	*-0,25725*			

Table 12: Kinetics results. The deviation of CP signals from the normative kinetics values (Hof et al., 2005; Winter, 2009) from typically developing children ('normative') of each variable was calculated by cross-correlation for every child's LIL and MIL separately pre- and post-intervention. Afterward, cross-correlation values "pre-post intervention" were compared by using the Wilcoxon sign rank test. This table shows an overview of Wilcoxon sign rank test (p-value) results, including effect sizes for all

variables across gait phases. Statistically significant results (p<0.05) are marked with yellow color. *Legend:* ES (effect size); More impaired limb (MIL); Less impaired limb (LIL); Initial contact (IC); Loading response (LR); Midstance (MST); Terminal stance (TS); Pre-swing (PSW); Initial swing (ISW); Midswing (MSW); Terminal swing (TSW).

7.3.4. Spatiotemporal parameters results

Generally, statistically significant differences were found in the vast majority of spatiotemporal parameters followed by moderate effect sizes (see Table 13). The most important changes were increased cadence; step length; step width and walking speed. On the other, there was significant decrease in time needed for double support; stride length and stride time. Table 13 summarizes spatiotemporal parameters quantitative changes including effect sizes for all children with CP. Furthermore, median values changes for variables that showed statistically significant differences are shown in Table 14.

Spatiotemporal parameters	Pre-post condition (p-value) / Effect size
Cadence MIL	0,0025
ES	0,569871
Cadence LIL	0,0038
ES	0,592474
Double support MIL	0,0004
ES	0,40032
Double support LIL	0,0004
ES	0,448359
Foot off MIL	0,0385
ES	0,6245
Foot off LIL	0,0063
ES	0,592474
Opposite foot contact MIL	0,1459
ES	0,116664
Opposite foot contact LIL	0,3876
ES	-0,288231
Opposite foot off MIL	0,3876
ES	-0,288231
Opposite foot off LIL	1,2255
ES	0,116664
Single support MIL	0,3876
ES	0,016013
Single support LIL	1,2255
ES	-0,034503
Step length MIL	0,0071
ES	0,6245
Step length LIL	0,0064
ES	0,560449
Step time MIL	0,04
ES	0,592474
Step time LIL	0,3876
ES	0,116664
Step width MIL	0,0366
ES	0,560449
Step width LIL	0,0274
ES	0,448359
Stride length MIL	0,0148
ES	0,592474
Stride length LIL	0,0312
ES	0,464372
Stride time MIL	0,0071
ES	0,576461
Stride time LIL	0,0064
ES	0,51241
Walking speed MIL	0,03548
ES	0,598912
Walking speed LIL	0,03267
ES	0,608487

Table 13: Spatiotemporal parameters results. Pre-post RAGT intervention spatiotemporal median values were compared by using the Wilcoxon sign rank test. It was calculated for every child's LIL and MIL separately. This table shows an overview of Wilcoxon sign rank test (p-value) results, including effect sizes for all variables. Statistically significant results ($p<0.05$) are marked with yellow color. *Legend:* ES (effect size); More impaired limb (MIL); Less impaired limb (LIL).

Spatiotemporal parameters	LIL median before	LIL median after	MIL median before	MIL median after
Cadence (steps/min)	109,558	112,450	109,042	111,575
Double support (s)	0,3725	0,3392	0,3692	0,3442
Foot off (%)	65,04	64,98	64,35	64,19
Opposite foot contact (%)	51,68	51,18	48,48	48,92
Opposite foot off (%)	16,67	15,08	13,88	13,60
Single support (s)	0,3967	0,3958	0,3917	0,3908
Step length (m)	0,4367	0,4567	0,4383	0,4642
Step time (s)	0,5542	0,5475	0,6033	0,5833
Step width (m)	0,1194	0,1247	0,1198	0,1213
Stride length (m)	0,8742	0,8367	0,8733	0,8508
Stride time (s)	1,16	1,13	1,17	1,14
Walking speed (m/s)	0,811	0,863	0,801	0,875

Table 14: Median values of spatiotemporal parameters results. Pre-post RAGT intervention spatiotemporal median values were compared by using the Wilcoxon sign rank test. *Legend:* More impaired limb (MIL); Less impaired limb (LIL).

7.4. Clinical tests results

Statistically significant ($p < 0.05$) pre-post RAGT intervention differences that indicate decreased joint contractures, increased selective motor control of lower extremities, and ability to walk farther distances were found.

7.4.1. Passive range of motion results

The most significant bilateral PROM changes were observed in hip and ankle joints followed by moderate effect sizes ranging between 0.432346 to 0.544436 (see Table 15). Generally, pathological contractures that were present in both joints pre-intervention decreased at least by 10°. Table 15 summarizes PROM quantitative changes including effect sizes for all children with CP. Examples of qualitative changes in PROM together with normative data from typically developing children are shown in Figure 24.

PROM	Pre-post condition (p-value) / Effect size
Hip extension MIL	increased by 10°(p=0.004)
ES	0,544436
Hip extension LIL	increased by 10°(p=0.004)
ES	0,544436
Hip internal rotation MIL	increased by 15°(p=0.002)
ES	0,608487
Hip internal rotation LIL	increased by 10°(p=0.002)
ES	0,51241
Hip external rotation MIL	increased by 5°(p=0.008)
ES	0,528423
Hip external rotation LIL	increased by 2.5°(p=0.043)
ES	0,432346
Knee popliteal angle unilateral MIL	increased by 5°(p=0.008)
ES	0,528423
Knee popliteal angle unilateral LIL	condition unchanged (p=0.246)
ES	0,208167
Knee popliteal angle bilateral MIL	increased by 5°(p=0.008)
ES	0,528423
Knee popliteal angle biilateral LIL	increased by 2.5°(p=0.043)
ES	0,432346
Knee extension LIL	decreased by 5°(p=0.035)
ES	0,528423
Knee extension MIL	decreased by 5°(p=0.004)
ES	0,528423
Ankle dorsiflexion with knee flexed MIL	increased by 10°(p=0.006)
ES	0,544436
Ankle dorsiflexion with knee flexed LIL	increased by 10°(p=0.006)
ES	0,544436
Ankle dorsiflexion with knee extended MIL	increased by 10°(p=0.006)
ES	0,544436
Ankle dorsiflexion with knee extended LIL	increased by 10°(p=0.006)
ES	0,544436

Table 15: PROM results. Pre-post RAGT intervention PROM values were compared by using the Wilcoxon sign rank test. It was calculated for every child's LIL and MIL separately. This table shows an overview of Wilcoxon sign rank test (p-value) results, including effect sizes for all variables. Statistically significant results (p<0.05) are marked with yellow color. *Legend:* ES (effect size); More impaired limb (MIL); Less impaired limb (LIL).
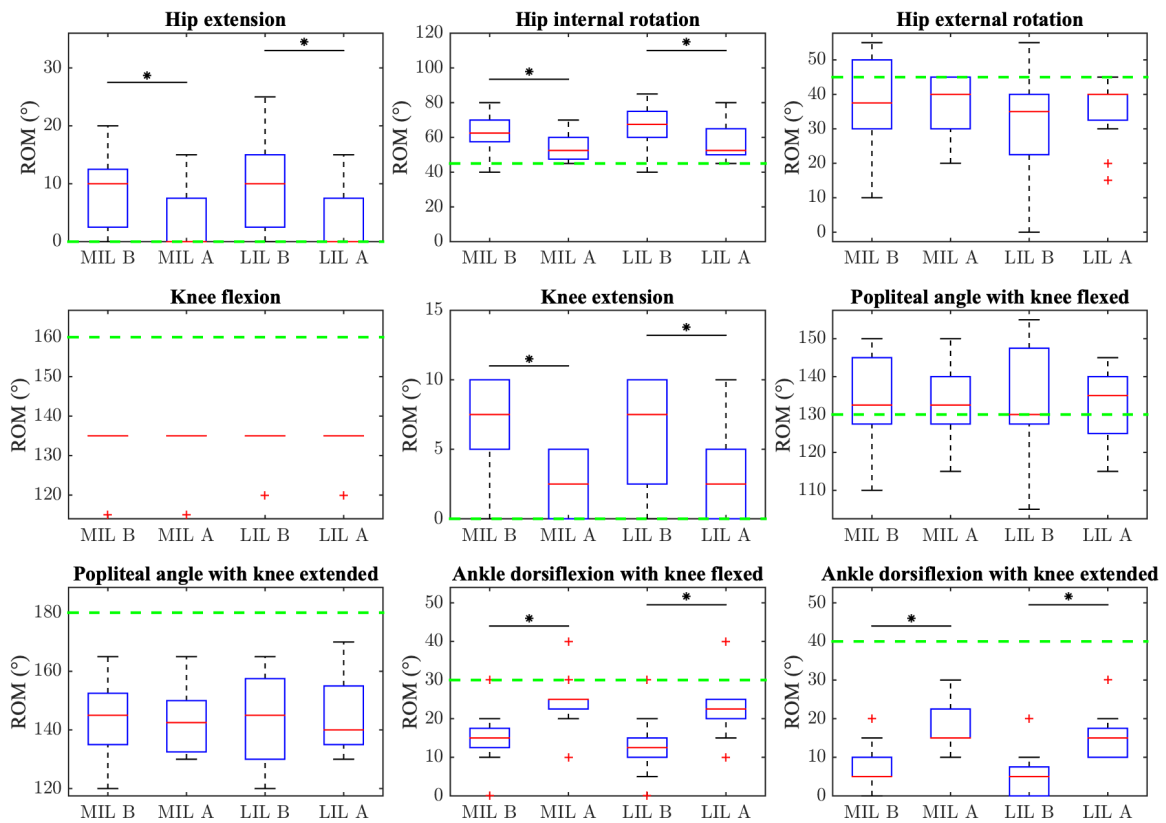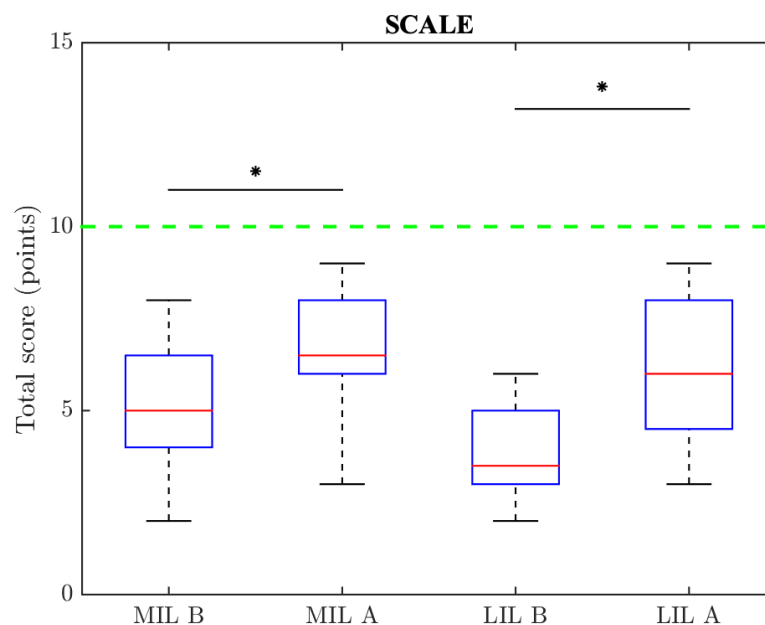
Figure 24: Qualitative pre-post intervention changes in PROM. The interpretation is as follows: box-plots represent the median values of all twelve children with CP for both MIL and LIL, pre and post-RAGT intervention (axis x). The green dotted line represents normative data (Katz et al., 1992) from typically developing children corresponding to the joint range of motion values expressed in degrees (°) (axis y). Statistically significant changes in the median values are marked with black *. *Legend:* Range of motion (ROM); More impaired limb before (MIL B); More impaired limb after (MIL A); Less impaired limb before (LIL B); Less impaired limb after (LIL A).

7.4.2. SCALE results

Total SCALE scores increased bilaterally and these findings were followed by moderate and small effect sizes ranging between 0.464372 to 0.592474 (see Table 16). Table 16 summarizes SCALE scores quantitative changes including effect sizes for all children with CP. Examples of qualitative changes in SCALE together with normative data from typically developing children are shown in Figure 25.

SCALE	Pre-post condition (p-value) / *Effect size*
Total score MIL	increased by 1.5 points (p=0.001)
ES	*0,464372*
Total score LIL	increased by 2.5 points (p=0.001)
ES	*0,592474*

Table 16: SCALE results. Pre-post SCALE scores values were compared by using the Wilcoxon sign rank test. It was calculated for every child's LIL and MIL separately. This table shows an overview of Wilcoxon sign rank test (p-value) results including effect sizes. Statistically significant results (p<0.05) are marked with yellow color. *Legend:* ES (effect size); More impaired limb (MIL); Less impaired limb (LIL).
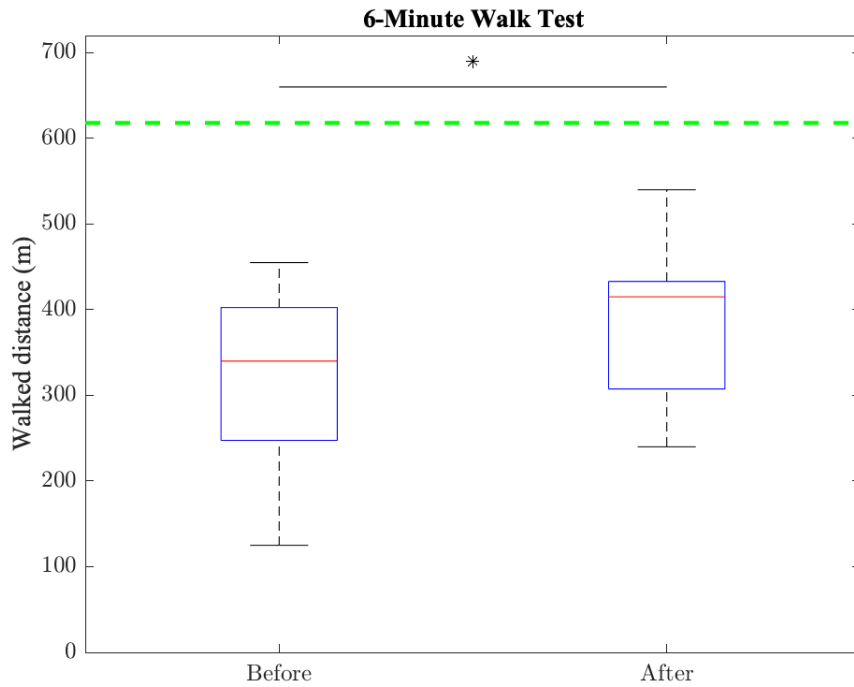
Figure 25: Qualitative pre-post intervention changes in SCALE scores. The interpretation is as follows: box-plots represent the median values of all twelve children with CP for both MIL and LIL, pre and post-RAGT intervention (axis x). The green dotted line represents normative data (Fowler, 2009) from typically developing children corresponding to the physiological SVMC expressed in points (axis y). Statistically significant changes in the median values are marked with black *. *Legend:* Selective Control Assessment of Lower Extremities (SCALE); More impaired limb before (MIL B); More impaired limb after (MIL A); Less impaired limb before (LIL B); Less impaired limb after (LIL A).

7.4.3. Six-minute walk test results

The 6MWT walking distance increased by 75 meters and this finding was followed by a strong effect size 0.6245 (see Table 17). According to Ulrich et al. (2013), the normative average distance of typically developing children is 618±79 meters. Table 17 summarizes SCALE scores quantitative changes including effect sizes for all children with CP. Examples of qualitative changes in SCALE together with normative data from typically developing children are shown in Figure 26.

6MWT	Pre-post condition (p-value) / Effect size
Total distance walked	increased by 75 meters (p=0.001)
ES	*0,6245*

Table 17: 6MWT results. Pre-post 6MWT total distance walked values were compared by using the Wilcoxon sign rank test. This table shows an overview of Wilcoxon sign rank test (p-value) results including effect size. Statistically significant results (p<0.05) are marked with yellow color. *Legend:* ES (effect size); 6-minute walk test (6MWT).

Figure 26: Qualitative pre-post intervention changes in 6MWT. The interpretation is as follows: box-plots represent the median values of all twelve children with CP for pre and post-RAGT intervention (axis x). The green dotted line represents normative data (Ulrich et al., 2013) from typically developing children expressed in meters (axis y). Statistically significant changes in the median values are marked with black *.

8. DISCUSSION

8.1. Research goals

This research study investigated whether RAGT can contribute to the improved quality of gait patterns in children with CP. The research study aimed to objectivize the effects that followed RAGT by a set of standardized, valid, and reliable methods such as CGA and clinical tests (PROM, SCALE, 6MWT). Finally, based on the research findings, the PI proposes indicators that either prove or disprove that RAGT improves the quality of gait pattern in children with CP.

8.2. Children with cerebral palsy

One of the most challenging tasks in every research is a creation of a homogeneous representative sample of subjects. A vast majority of existing RAGT studies is based on small samples and heterogeneous groups of children with CP in terms of topographic and GMFCS classifications (Meyer-Heim et al., 2009; Wallard et al. 2012; Meyer-Heim and van Hedel, 2013; Wallard et al., 2014; Beretta et al., 2015; Aurich-Schuler, 2017; Ricklin et al., 2018; Beretta et al., 2020). This is also a widely discussed topic among clinicians, and one of the main reasons why research findings of existing RAGT studies cannot be easily generalized to a wider spectrum of the CP population (Aurich-Schuler et al., 2015). Based on that learning experience, this research aimed to create the as homogenous group as possible. For that, inclusion criteria were limited to spastic diparesis type of CP and GMFCS groups I-III as these children can ambulate for at least short distances. In this research out of twelve ambulatory children with CP - two children were at GMFCS I, six children were at GMFCS II, and four children were at GMFCS III level. The vast

majority of children with CP had toe walking patterns (n=10) and only two children with CP had crouch gait patterns. Although this research study aimed to enroll a much higher number of subjects (e.g. at least 30 children with CP), only twelve children met all inclusion criteria and were able to follow an intense 4-week RAGT program in 20 consecutive working days. This research study enrolled only twelve children with CP, yet the group can be considered homogeneous in terms of topographic and GMFCS classifications compared to previous RAGT studies (Meyer-Heim et al., 2009; Wallard et al. 2012; Meyer-Heim and van Hedel, 2013; Wallard et al., 2014; Beretta et al., 2015; Aurich-Schuler, 2017; Ricklin et al., 2018; Beretta et al., 2020).

8.3. Uncontrolled study

At the execution phase of this research study, it was impossible to create another control group that would meet the same inclusion criteria and conduct controlled intervention program that would be relevant for the main purpose of the research study (e.g. comparison of RAGT with different gait training method, etc.). Despite that, the data of children with CP were compared with normative data of healthy controls (CGA and clinical tests normative data). Since comparison with a group of healthy children that underwent CGA in the same gait laboratory and clinical tests would be desirable, it was impossible to find typically developing children that would voluntarily undergo all the procedures in URIS. Furthermore, data comparison of children with CP and normative sets is routinely used in both CGA and clinical tests for clinical decision-making in daily practice among clinicians.

8.4. Robot-assisted gait training as a monotherapy

The purpose of this research study was to investigate the quantitative and qualitative effects of RAGT as monotherapy and to observe to what kind of extent this method can contribute to gait neuroplasticity in children with CP. In this research study, RAGT was not combined with conventional physiotherapy or other approaches to avoid misinterpretation of results. However, some of the existing RAGT studies (Meyer-Heim et al., 2009; Meyer-Heim and van Hedel, 2013; Beretta et al., 2015; Beretta et al., 2020) reported on the combination of this method with conventional physiotherapy as this captures the daily situation among clinicians that provide care to children with CP. Despite that, the results of existing studies (Meyer-Heim et al., 2009; Meyer-Heim and van Hedel, 2013; Beretta et al., 2015; Beretta et al., 2020) should be interpreted carefully and cannot be generalized as too many factors might influence the overall clinical outcome.

8.5. Justification of CGA data processing and statistical evaluation

This research did not only aim to explore statistically significant differences (quantitative) but mainly to explore whether differences indicate that RAGT can improve the quality of gait patterns in children with CP. Evaluation of CGA data included signal processing and statistical evaluation. Furthermore, it was important to choose such an evaluation approach that would not devalue the signal. As could be seen in Figure 11, the deviation CP signals from the normative values were calculated by NCC. Generally, cross-correlation (CC) is a conventional approach that is used to compare signals including their shapes. Wren et al. (2006) proposed to apply NCC for comparing EMG signal amplitudes during walking.

Recently, the NCC method has been used to scrutinize synergy measures based on surface EMG profiles (Zwaan et al., 2012), the relationship between the symmetry of gait and that of muscular activity (Syczewska and Świecicka, 2016), and the correlation between muscle activation while walking forwards and backwards (Mahaki et al., 2017). Moreover, the NCC was proposed to assess angular rate symmetry (Gouwanda and Senanayake, 2011). Properties of symmetry or similarity with abnormal gait signals sensitivity to shape differences, scaling, and shift that should be taken into consideration. Sensitivity to shape testifies how well a given measure can quantify the difference of a signal shape (changes in magnitude throughout the gait cycle). Scaling refers to whether or not a given measure detects scaled signals, e.g. signals are the same shape but the values are n-times lower or higher. A shift is to be understood as the change in amplitude, e.g. the two signals with identical shapes are shifted when having a different mean value. All three properties, namely the sensitivity to shape, scaling, and shift differences, should be considered when comparing abnormal gait with normative signals. The NCC approach meets the shape and shift criteria. Based on literature research and empirical experience, the NCC was chosen as it met the criteria needed to evaluate the CGA signals reliably and objectively (Wren et al., 2006, Kaso, 2018).

8.6. The key findings of the research study

The key findings of the research study suggest that RAGT as monotherapy can induce more physiological muscle activity and joint kinematics trajectories, more economic energy expenditure in spatiotemporal gait parameters, increased SVMC, walking farther distances, and decreased joint contractures in CP children with spastic diparesis. Individual findings of variables are discussed below.

Despite statistically significant changes, only with a deeper analysis of the gait cycle profiles and clinical tests, the results of the research study could be understood comprehensively. For that, it is strongly suggested to observe and compare changes in CGA and clinical test variables when considering any further directions of treatment/surgical management and clinical decision-making. Based on the findings, the H0: '*Gait pattern of children with CP will remain unchanged following RAGT intervention'* was rejected.

8.7. Interpretation of CGA results

8.7.1. Interpretation of sEMG results

The following chapter provides a discussion on confirmed *H1: 'RAGT will induce a more physiological sEMG muscle activity by the means of approximation to the normative curve'.*

As this study enrolled CP children with spastic diparesis, the significant improvement was found mainly in bilaterally decreased muscle activity which tends to show a more physiological activation trend when compared to the normative curve (Hof et al., 2005; Winter, 2009). Since active training seems to be more effective than passive training for motor learning and cortical reorganization in central motor impairments, RAGT likely improved muscle activation of children with CP due to active training performed with a high-repetition rate of guided movements (Meyer-Heim et al., 2009; Aurich-Schuler, 2017). Although this research study did not explore spasticity in children with CP, it could be one of the supportive explanations why RAGT led to the decrease of muscle activity. Cyclic motion has been reported to be effective in decreasing spasticity in stroke patients (Monaghan, 2017).

Rectus femoris

According to Perry (2010), the RF should be active during the swing phase, functioning as a hip flexor, but it should also be active during the stance phase as a knee extensor. In children with CP, the RF muscle tends to be shortened and very often spastic. This leads to flexion contractures that do not allow active and controlled knee extension during the stance phase. Therefore, children with CP can hardly differentiate between flexion and extension movements during stance and swing phases (Lee and Hidler, 2008; Fowler, 2009). Although findings of this research study showed the bilaterally decreased activity of RF almost across all gait cycle phases, the trend of non-physiological muscle activity curve is still present. Therefore, this change was considered only a quantitative improvement. However, it is worth elaborating on parameters of RAGT protocol such as increased number of treatments (e.g. up to 40) such as in the study of Verazaluce-Rodriguez et al. (2014) to explore whether it is possible to induce more physiological RF muscle activity in a longer period time.

Biceps femoris

As a biarticular muscle, the BF is mostly active during mid-swing and continues to be active up to mid-stance as a hip extensor and knee flexor (Perry, 2010). However, in children with CP, the BF is typically weakened due to the dominant activity of the antagonist RF muscle (Goldberg et al., 2012). In this research study, all CP children with spastic diparesis had increased activity of BF muscle before the RAGT intervention. Bilaterally decreased activity of BF that tends to show more physiological activation trend when compared to the normative curve was found

post-intervention (Hof et al., 2005; Winter, 2009). Therefore, this change was considered a quantitative and a qualitative improvement.

Tibialis anterior

The typical onset of TA activation starts before pre-swing and continues up to the loading response phase (Perry, 2010). As children with CP often have spastic calf muscles and foot deformities, they often have difficulty performing dorsiflexion and foot inversion resulting in a lack of TA activity (Brunner et al., 2008). In this research study, the TA was observed to be mainly active post-intervention during pre-swing, initial swing, and terminal swing up to the loading response phase as previously shown in studies performed on healthy subjects (Hidler, 2005). Thus, findings indicate that RAGT can enhance the physiological activity of TA, although the ankle joint during RAGT is only passively positioned to the neutral position (Colombo, 2000; Kolář, 2002). This is an interesting finding because it indicates that perhaps the active support and active movement of the proximal musculature may help encourage a similar adaptation in the distal musculature despite a lack of active support (Radziminska,2012). Furthermore, the curve of CP children tends to show a more physiological activation trend when compared to the normative curve (Hof et al. 2005; Winter, 2009). This change was considered a quantitative and a qualitative improvement. Nevertheless, TA activity appeared more silent in the loading response compared to the normative curve (Hof et al., 2005; Winter, 2009). The same finding was reported by Hidler et al. (2005) in adult patients who explained that foot lifters probably contributed to the decreased TA activity. In this research study the tension of the foot-lifers was adjusted according to the needs of every child with CP

individually; enough for good foot clearance during the swing phase, but not too strong to make the ankle joint stiff.
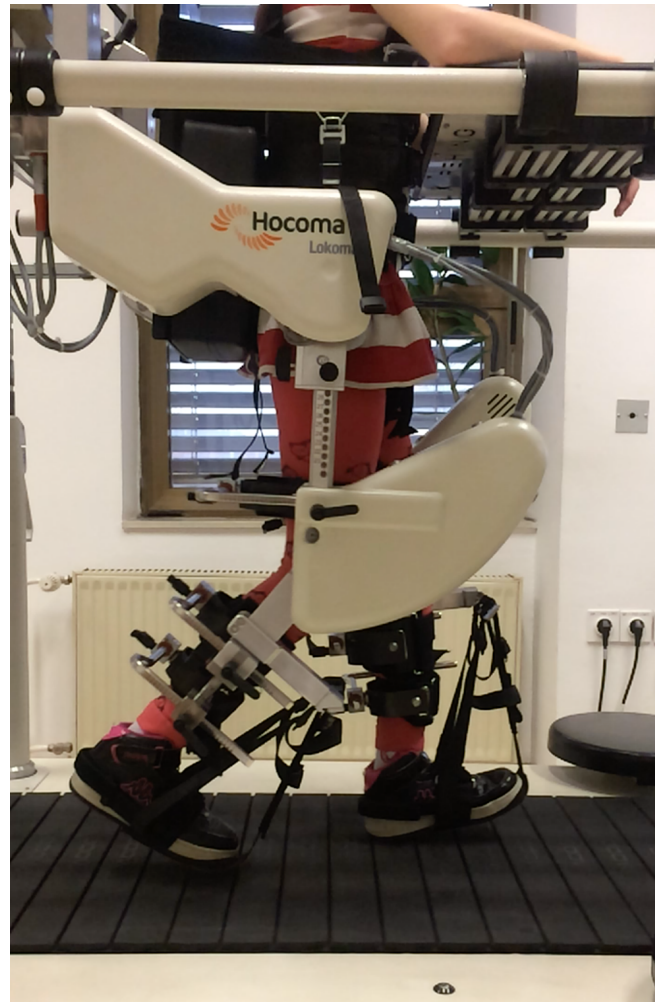
Figure 27: An 11-year-old girl with spastic diparesis during RAGT - see foot lifters (source: own).

Medial gastrocnemius

The MG is a biarticular muscle that performs plantar and knee flexion. Physiological activation of MG starts at mid-swing and continues to increase at terminal stance and pre-swing. This muscle is typically spastic (Katz, 1989) and causes shortening of the Achilles tendon which can result in contracture and foot deformities (Perry, 2010).

Generally, calf muscles are considered the main contributors to abnormal gait patterns negatively influencing both ankle and knee joints (Patikas et al., 2007; Stewart and Shortland, 2010). Therefore, if the MG muscle is influenced, either by stretching, relaxation, or positioning the affected joint in the neutral position, it can contribute to the increased range of motion in the ankle joint, as well as it can reciprocally allow the antagonist TA muscle to activate (Colombo et al., 2000; Katz et al., 1989). This was assumed to be the principle of how the RAGT affects the ankle joint and its surrounding muscles. Findings showed the decreased activity of MG mainly in terminal stance, mid-swing, and terminal swing phases. Furthermore, the curve of CP children tends to show a more physiological activation trend when compared to the normative curve (Hof et al., 2005; Winter, 2009). This change was considered a quantitative and a qualitative improvement.

8.7.2. Interpretation of intermuscular correlations

Moderate to strong correlations were found bilaterally among agonist-antagonist pairs in terms of their more physiological activation but only in terminal swing and midswing. In the vast majority of other gait phases, correlations were observed mainly in the MIL. One of the possible explanations is that RAGT potentiated the use of MIL that generally has worsened SVMC as has been also shown in the SCALE scores. It could be explained through the stimulation of the side that appear more silent such as in hemiplegic patients. Apart from previously explained reasons that led to more physiological muscle activation, BWS is one of the directly linked parameters to muscle activity during RAGT, and therefore should be carefully indicated to avoid pathologic couple movements in lower limbs.

Bonikowski and Mrozek (2012) explored the effects of BWS in 10 children with CP that underwent RAGT with and without 30% BWS. The sEMG of RF and semitendinosus muscles was recorded 15 minutes post-training. A significant increase in EMG activity was observed in the group without BWS. These results indicate the importance of loading the patient to enhance muscle activity. In this research study, the BWS typically started with 50% unloading and was gradually decreased to 30% of children's body weight. Considering the positive effects noted in the present study combined with previous results showing that less BWS yields greater sEMG improvement. Future studies should investigate longer-duration RAGT protocols whereby the amount of BWS can be continually reduced over time, which would hypothetically improve muscle activation and coordination to an even greater extent.

8.7.3. Interpretation of joint kinematics results

The following chapter provides discussion on H2: *'RAGT will induce more physiological joint kinematics trajectories by the means of approximation to the normative curve'.* This hypothesis was confirmed only for variables hip rotation; foot progress angle; thorax tilt and knee abduction-adduction.

Generally, there is a lack of studies that explored the effect of RAGT on joint kinematics in children with CP. However, the interpretation of existing research is rather controversial due to various factors such as heterogeneity of GMFCS, or monotherapy approach versus a combination of RAGT with conventional physiotherapy. For example, Beretta et al. (2015) and (2020) suggested that combined programs of RAGT and conventional physiotherapy induce improvements in functional activities and gait patterns in children and adolescents with acquired

brain injury. This study also reported a statistically significant increase in hip extension during the terminal stance and swing phase. However, it should be highlighted that this study combined RAGT with conventional physiotherapy. A recent study conducted by Cherni et al. (2020) that enrolled 24 children with CP (GMFCS II-IV) concluded no significant changes in kinematic patterns. These results might be influenced by a wide spectrum of GMFCS groups, as well as group IV typically embraces the most severe cases of CP and children who cannot ambulate. Druzbicki et al. (2013) concluded from a controlled study on fifty-two CP children with spastic diplegia (GMFCS II-III) statistically insignificant changes among groups following Lokomat + physiotherapy, and physiotherapy only. However, a significant improvement in the maximal range of hip joint flexion (p=0.0065) was found. One of the used explanations was the patient's passivity during the RAGT sessions. Wallard et al. (2014) highlighted a significant improvement in knee and ankle sagittal kinematics as well as dynamic balance control following RAGT combined with virtual reality in CP children who walk in jump gait pattern after the same RAGT TP as was used in the present study. To the best of the PI's knowledge, this is the first study reporting on changes that followed RAGT in hip rotations, foot progress angles, and thorax tilt. It is assumed that RAGT likely improved the joint kinematics due to a high repetition rate of guided movements in the most neutral position and joint centered position of the pelvis and lower limbs.

Pelvic kinematics

In this study, the Lokomat Pro device with a fixed pelvis module was used. Therefore, physiological movements such as contralateral pelvic drop, transverse rotation, and lateral translation were not allowed. Recently, it has been reported on an optional FreeD pelvic module that allows for more physiological pelvic movement during Lokomat training (Schuler et al., 2017). However, this module was not available at our URIS. The lack of physiological pelvic movements during RAGT can be an explanation for non-responsiveness in pelvic kinematics variables in this research study.

Hip joint kinematics

Although RAGT promotes guided movements in the sagittal plane, there were no significant changes in hip flexion-extension nor abduction-adduction movements such as previous findings by Druzbicki et al. (2013) or Wallard et al. (2017). Nevertheless, a bilateral decrease of pathologic internal hip rotations almost across all gait cycle phases was found. Furthermore, the curve of CP children tends to show a more physiological activation trend when compared to the normative curve (Hof et al., 2005; Winter, 2009). This has not been previously reported because RAGT does not allow hip rotation movements. As all children with CP that were enrolled in this study had toe walking patterns with dominant internal hip rotation, the RAGT orthoses allowed for setting the hip joint in the highest possible neutral position - the so-called "joint centered position" (Kolář, 2002; Žarković and Šorfová, 2017) followed by repetitive task-specific guided leg movements (see Figure 28). This is assumed to be an explanation of quantitative and qualitative changes that followed RAGT intervention.
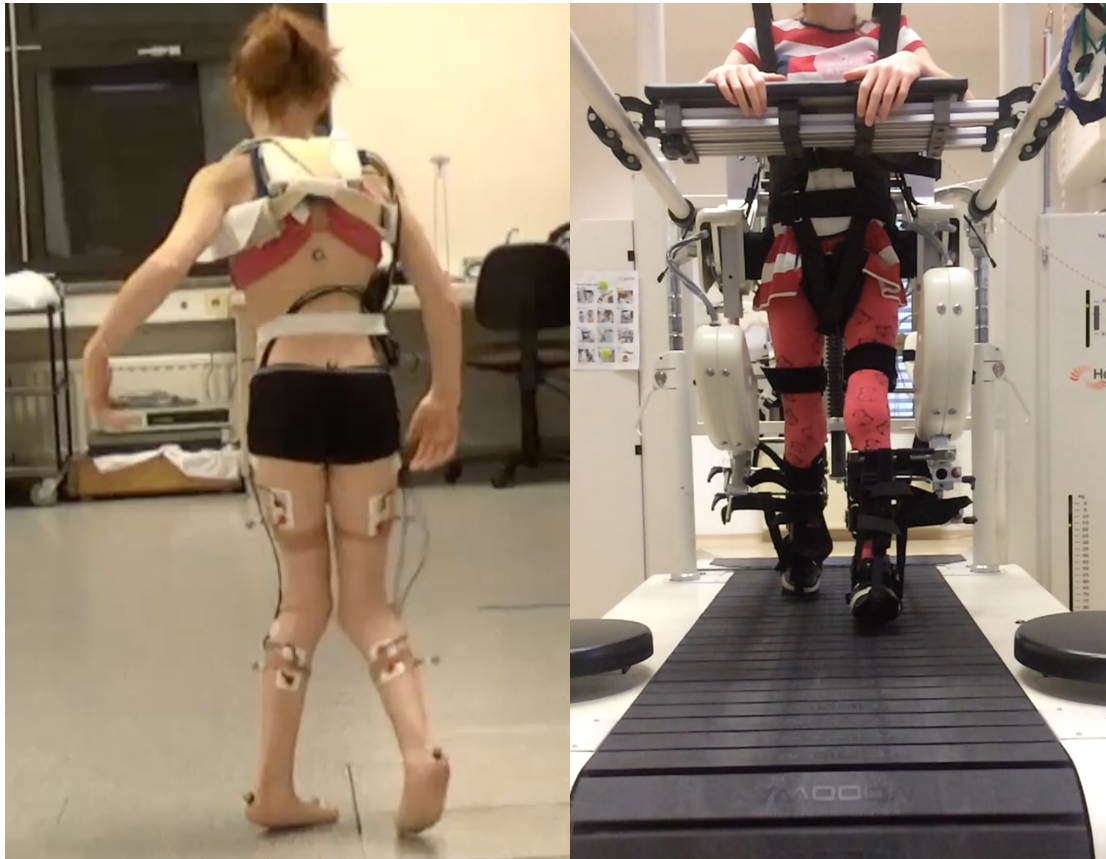
Figure 28: An 11-year-old girl with spastic diparesis ambulating in crouch gait pattern with dominantly spastic hip adductors (left). The same girl during RAGT ambulating in neutral and joint centered position of lower extremities and with extended posture (source: own).

Knee joint kinematics

Knee sagittal plane kinematic trajectories remain unchanged. The only quantitative change was observed unilaterally, mainly in MIL, in the knee abduction-adduction trajectory. We attribute this change to be related to the same mechanism as in hip rotation. Toe walking pattern combined with increased internal hip rotations leads to the valgus knee.

RAGT orthoses allow for setting the knee joint in a neutral position. Task-specific guided leg movements in neutral and joint centered position are assumed to be the possible explanation for this change (Kolář, 2002; Žarković and Šorfová, 2017).

Ankle joint kinematics

RAGT has no active ankle joint orthosis but allows only for passive fixation by using straps in a neutral position (Colombo et al., 2000). The passive fixation seems to be an explanation for unchanged trajectories of ankle joint flexion-extension and previously discussed the silent activity of TA muscle. As foot progress angle is directly linked to the position of the knee and hip joints (Perry, 2010), we assume that a quantitatively significant decrease of in-toeing is a result of the neutral and joint centered position of hip and knee could be set during RAGT (Kolář, 2002; Žarković and Šorfová, 2017). Furthermore, fixation straps at least allow for fine-tuning the ankle joint and toes position.

Thorax kinematics

A quantitatively significant decrease of anterior tilt was found bilaterally, however with more accent on the less impaired side of the trunk. This is assumed to be the result of multiple factors such as the ability of the child to actively extend the posture and BWS enhancement. Extended posture was enhanced by an additional armrest which is not standard RAGT equipment, yet it greatly contributed to an upright posture during gait therapies. RAGT TP parameters were always adjusted in such a way so that child can walk comfortably with extended posture and in the highest possible neutral and joint centered position of lower limbs. It was shown by Wallard (2017)

that RAGT can induce a more appropriate control of the upper body which is associated with an improvement of the lower limbs' kinematics.
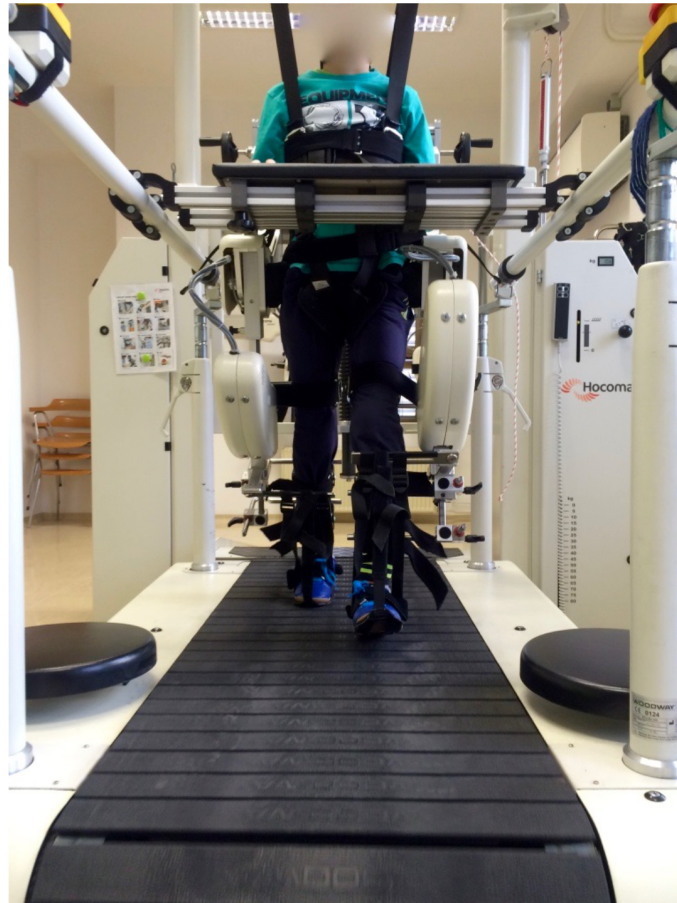
Figure 29: A 10-year-old boy with spastic diparesis during RAGT using an additional armrest for extended posture (source:own).

8.7.4. Interpretation of kinetics results

The following chapter provides a discussion on rejected H3: *'RAGT will induce a more physiological gait kinetics by the means of approximation to the normative curve'.*

Joint kinetics is a component of CGA gait analysis and should be interpreted with all other information such as joint kinematics, sEMG, spatiotemporal variables, and pertinent clinical tests such as PROM.

Joint kinetics provides an opportunity to understand better the role of the trunk and inter-joint relationship during gait (Perry, 2010; Armand et al., 2016). For example, the evaluation of the relationship of power generation among involved versus the non-involved side of hemiplegia patients suggests that the non-involved limb shows greater than normal power generation to compensate for the weaker non-involved limb. In general, when using joint kinetics, emphasis should be made on the pattern and timing of the specific curve in comparison to normative with less emphasis on the amplitudes of the individual peaks as suggested by Davis et al. (1991). This research study reported no quantitative nor qualitative improvements in kinetics variables that would be clinically relevant for children with CP. Furthermore, the vast majority of kinetic variables remained unchanged pre-post intervention which only suggests that RAGT has no or very low impact on kinetic variables with persistent dominance of the handicap. As there is a lack of studies that explored the effect of RAGT on kinetics in children with CP, the findings of this research study cannot be generalized but rather considered a suggestion. The PI leaves space for improvement and exploration in a greater clinical trial.

8.7.5. Interpretation of spatiotemporal parameters

The following chapter provides discussion on confirmed H4: *'RAGT will enhance the ability of children with CP to walk farther distances'.*

Definition of spatiotemporal parameters allows for an objective definition of where, when, how long, and how rapidly the individual is in contact with the ground (Perry, 2010; Baker, 2013; Armand et al., 2016). In this research study, the most important changes were observed in increased cadence; step length; step width, and walking speed.

On the other, there was a significant decrease in time needed for double support; stride length and stride time. The combination of increased cadence and walking speed together with decreased stride length and time reflects that children with CP take a high number of smaller steps, they walk faster and in a shorter period. This could potentially contribute to more economic energy expenditure, especially if ambulatory children with CP need to walk farther distances. Similar findings were reported by Beretta et al. (2015). Improved spatiotemporal parameters are also supported by the ability to walk farther distances as has been shown in the results of 6MWT.

8.8. Interpretation of clinical tests

Clinical tests are an integral part of comprehensive evaluation in children with CP. This research study aimed to choose such evaluation methods that are valid, standardized, and reliable. Apart from PROM and walk test which capture the quantitative effect of RAGT, the PI emphasized the evaluation of SVMC which has great clinical importance on SVMC, yet it is not routinely assessed. To the best of the PI's knowledge, this is the first study suggesting that RAGT improves SVMC in children with CP.

8.8.1. Interpretation of passive range of motion results

The following chapter provides a discussion on confirmed H5: *'Children with CP will increase the PROM in all joints following RAGT intervention'*.

It is common to observe a decreased PROM following a neurological injury. The PROM is assessed to determine the mobility of a joint regardless of the voluntary ability of the patient and it is usually slightly greater than active ROM and much

greater in case of muscle weakness. The most important results were increased hip extension and ankle dorsiflexion together with decreased internal hip joint rotation. RAGT improved the PROM due to a high repetition rate of guided movements in the most neutral and joint-centered position of the pelvis and lower limbs (Kolář, 2002; Žarković and Šorfová, 2017). The findings of this research study are consistent with Vrečar et al. (2013) and indicate that RAGT can be an effective method for improving the PROM of lower extremities in spastic diparesis children with CP.

8.8.2. Interpretation of SCALE results

The following chapter provides discussion on confirmed H6: *'Children with CP will show higher ability to perform selective movements of hip, knee, and ankle joint following RAGT intervention'*.

The latest research suggests that SVMC represents an important factor affecting functional movement tasks including gait, and maybe an indicator of the improvement following therapeutic or surgical interventions (Clowry, 2007; Goldberg et al., 2012, Balzer et al., 2015. Despite clinical findings, SVMC has not been explored as a determinant factor of gait biomechanics in CP children (Fowler et al, 2009). Children with CP have reduced ability to develop skilled intra-limb coordination movements and may develop movement strategies that retain primitive coupled patterns manifesting as an inability to dissociate hip and knee recruitment when ambulating (Fowler et al., 2009; Perry et al., 2010). Coupled movements were also observed in all children with CP that were enrolled in this research study. SVMC is also strongly associated with postural control and stability. Structural brain damage in children with CP can generate an irrelevant motor program leading to abnormal posture (Farmer et al., 2008; Chruscikowski, 2017).

Therefore, SVMC of children with CP can be effected either by demanding (e.g. standing, walking) or non-demanding postural positions (e.g. sitting, lying) (McMulkin et al., 2000; Desloovere et al., 2006). This is the first research study that reported improved SVMC following RAGT in CP children with spastic diparesis. One of the possible explanations why children with CP improved their SCALE scores can be due to posturally non-demanding testing positions. Nevertheless, in this research study, there were no significant changes in sagittal plane joint kinematics in children with CP that would indicate the change of coupling movements among hip, knee, and ankle joints. The findings of this research study indicate that improvement of SVMC in spastic diparesis children with CP can be possible. However, this research study leaves space for improvement in terms of further investigation into how can RAGT improve SVMC in children with CP when ambulating.

8.8.3. Interpretation of 6MWT results

The following chapter provides discussion on confirmed H4: *'RAGT will enhance the ability of children with CP to walk farther distances'*.

The 6MWT is a reliable and valid test for assessing endurance, functional abilities, and outcomes in children with CP. The minimal clinically relevant difference in 6MWT has been estimated as 54 meters (Redelmeier, 1997). Children with CP in this research study had a pre-intervention median value of total distance walked 350 meters which was increased by 75 meters post-intervention to the median value of 425 meters. The findings of this research study are consistent with Beretta et al. (2015) and Beretta et al. (2019) and indicate that RAGT can be an effective method

for improving the walking endurance in spastic diparesis children with CP following RAGT.

8.9. Conclusion on scientific question and hypotheses

This research study aimed to answer if 'RAGT can induce a more physiological gait in ambulatory children with CP that would be comparable with healthy children?'. Based on confirmation/rejection of several hypotheses, the key research findings were that RAGT induced more physiological muscle activity and joint kinematics trajectories, more economic energy expenditure in spatiotemporal gait parameters, ability to walk farther distances, increased SVMC ability, and decreased joint contractures. Research findings can be observed from two perspectives:

- findings indicating a more physiological gait due to potential effect on neuroplasticity (sEMG, joint kinematics, SVMC)

- findings indicating functional changes in passive structures and walking capacities that contributed to the overall gait improvement (PROM, spatiotemporal gait parameters, walking farther distances)

RAGT principle is based on intensive, task-specific, and high-repetition-rate of guided movements which contribute to the motor learning process and cortical reorganization (Krishnan, 2019). However, this research study brings to the fore and assumes additional factor that greatly contributes to a more physiological gait pattern of children with CP - centered position of joints. In conditions with impaired motor control, such as in children with CP, joints are in a so-called decentralized position.

At the same time, a decentralized joint position also contributes to improper muscle function. The centered joint position allows for optimal loading of the joint in both static and dynamic conditions, as well as it enhances physiological and economic muscle patterns. This is an interesting finding because it indicates that the combination of task-specific guided movements in a high-repetition-rate, and centered position of joints resulted in a more physiological gait pattern in children with CP. This phenomenon was mostly accented in this research study by a more physiological muscle activation and joint kinematics during gait and static PROM evaluation. Based on findings, it is assumed that RAGT affects motor control by improving functional movement pattern chains which results in a more physiological gait pattern. Indisputably, changes that were observed in gait patterns, SVMC, and walking capacity must reflect the RAGT effect on the CNS. However, such assumption should be confirmed by neuro-imaging methods (e.g. functional magnetic resonance imaging). This study leaves space for improvement in terms of adding neuro-imaging methods which were not available to the PI at the time of this research study.

H0 - rejected	The gait pattern of children with CP will remain unchanged following RAGT intervention.
H1 - confirmed	RAGT will induce a more physiological sEMG muscle activity by the means of approximation to the normative curve.
H2 - confirmed only for variables hip rotation; foot progress angle; thorax tilt and knee abduction-adduction.	RAGT will induce more physiological joint kinematics trajectories by the means of approximation to the normative curve.
H3 - rejected	RAGT will induce more physiological gait kinetics by the means of approximation to the normative curve.
H4 - confirmed	RAGT will enhance the ability of children with CP to walk farther distances.
H5 - confirmed	Children with CP will increase the PROM in all joints following RAGT intervention.
H6 - confirmed	Children with CP will show a higher ability to perform selective movements of hip, knee, and ankle joint following RAGT intervention.

Table 18: Overview of confirmed/rejected hypotheses.

9. CONCLUSION

CP is considered a condition primarily impacting motor control and movement. Children with CP have varying degrees of muscle weakness, spasticity, decreased SVMC, impaired coordination that limit functional capacity during walking. Because gait abnormalities affect community integration and quality of life, a priority of physiotherapy is to improve gait. After almost three decades RAGT devices are nowadays routine constituent in the gait rehabilitation of adults and pediatric patients. This is the first research study where was shown that RAGT as monotherapy can contribute to a more physiological gait in ambulatory children with CP with spastic diparesis (GMFCS I-III). The most important indicators of gait changes in children with CP were more physiological muscle activity and joint kinematics trajectories followed by increased SVMC and decreased joint contractures. Additionally, these findings were supported by increased ability to walk the farther distance with more economic energy expenditure. This is the first research study that extended the explanation of RAGT and its contribution to the improved quality of gait pattern by centered joint position. Considering that such changes can be achieved with RAGT as a monotherapy, this method indisputably deserves to be an integral part of pediatric gait rehabilitation. The PI is aware of study limitations such as the small sample size, uncontrolled trial, and lack of long-term follow-up data. For that, there is no tendency from the side of the PI to overemphasize and generalize the study results to a wider spectrum of the CP population. However, this research study provides a foundation on which future studies can be built as RAGT should be investigated over longer periods in different populations to further determine its effectiveness.

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13. APPENDIX

13.1. Ethics Committee approvals

CHARLES UNIVERSITY IN PRAGUE
FACULTY OF PHYSICAL EDUCATION AND SPORT
José Martího 31, 162 52 Praha 6 -Veleslavín
tel. +420 2 2017 1111
http://www.ftvs.cuni.cz/

Application for Ethics Board Review

Postgraduate research

Project title: Applied neurobiomechanical principles in robotic assisted gait training in pediatric neurorehabilitation

Nature of the research project: postgraduate research study for dissertation thesis

Author (chief investigator): **Dragana Žarković, M.Sc.**

Supervisor (in case of student research): **assoc. prof. Monika Šorfová (doc. Ing. Monika Šorfová, PhD.)**

Research project description: This research serves as a main part of the student's dissertation thesis. The aim of the research is to investigate therapeutic effect of the Lokomat device on the selective voluntary movement control in the lower extremities in pediatric patients with bilateral spastic cerebral palsy.

Guaranteed safety to be judged by experts:
Chief investigator guarantees that all methods used in the research are non-invasive and will not cause any harm to the patient nor to the expert.

Ethical aspects of the research:
Chief investigator guarantees that all personal data, ID and face of the subject will certainly not be presented in the public.

Informed consent (attached)
All subjects (and their parents or guardians) have read and signed the informed consent.

Date: July 31, 2015 Author's signature: Dragana Žarković, M.Sc.

Faculty of Physical Education and Sport, Charles University in Prague
ETHICS BOARD REVIEW

Ethics Board members: Prof. Ing. Václav Bunc, CSc.
Prof. PhDr. Pavel Slepička, DrSc.
Doc. MUDr. Jan Heller, CSc.

The Ethics Board at the Faculty of Physical Education and Sport, Charles University, approved the research project. aa

Approval number: 120/2015
Date: 12. 8. 2015

The Ethics Board at the Faculty of Physical Education and Sport, Charles University, reviewed the submitted research project and **found no contradictions with valid principles**, regulations and international guidelines for biomedical research involving human subjects.

The chief investigator of the project met the necessary requirements for receiving the Ethics Board approval.

UNIVERZITA KARLOVA v Praze
Fakulta tělesné výchovy a sportu
Official school stamp 2 52 Praha 6

Signature, REB Chairman

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Mag. Katja Groleger Sršen, dr. med..
-   tu;

Datum: 5. oktober 2015

Spoštovani!

Komisija za medicinsko etiko je na seji dne 5. oktobra 2015 obravnavala vlogo za mnenje o etični ustreznosti raziskovalnega projekta »Applied neurobiomechanical principles in robotic assisted gait training in pediatric neurorehabilitation« mag. Dragane Žarković pod mentorstvom prof. Monike Šorfove in somentorstvom mag. Katje Groleger Sršen, dr. med., in odgovorne zdravnice mag. Katje Groleger Sršen, dr. med..

Člani komisije za medicinsko etiko so menili, da je raziskovalni projekt »Applied neurobiomechanical principles in robotic assisted gait training in pediatric neurorehabilitation« mag. Dragane Žarković pod mentorstvom prof. Monike Šorfove in somentorstvom mag. Katje Groleger Sršen, dr. med. in odgovorne zdravnice mag. Katje Groleger Sršen, dr. med., etično ustrezen ob sodelovanju strokovnih sodelavcev teama za kineziološko analizo.

Predsednica komisije za medicinsko etiko URI-Soča:
prim. Tatjana Erjavec, dr. med.

13.2. Written informed consent forms

Informed Consent form for subjects and their parents taking part in the research study

Dragana Žarković, M.Sc., a physical therapist a student of a PhD. program Biomechanics at Charles University, Faculty of Sport and Physical Education, Prague, Czech republic

in cooperation with

University Rehabilitation Institute of Republic Slovenia, Children's Department of Rehabilitation

POSTGRADUATE DOCTORAL RESEARCH STUDY

on

"Applied neurobiomechanical principles in robotic assisted gait training in pediatric neurorehabilitation"

This Informed Consent Form is for children's subjects (signed by their parents or guardians) who attend University Rehabilitation Institute of Republic Slovenia, and who are invited to participate in the postgraduate doctoral research study on children with cerebral palsy.

Introduction

Dear children, parents and guardians,

my name is Dragana Žarković. I am a physical therapist and a PhD. student of Biomechanics at Charles University, Faculty of Sport and Physical Education in Prague, Czech republic. In cooperation with University Rehabilitation Institute of Republic Slovenia, Children's Department of Rehabilitation, I have created the postgraduate doctoral research study on children with cerebral palsy and robotic assisted gait training. I am going to give you information and invite you to be part of this research. You do not have to decide today whether you will participate in the research. Before you decide, you can talk to anyone you feel comfortable about the research. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, please, feel free to ask.

Purpose of the research

Children with cerebral palsy (CP) have problem with production of selective voluntary movements. They have reduced ability to develop the skilled movements - such as walking. It has been suggested that ability to move selectively especially in the lower extremities (legs) is an important predictor of improvement in therapeutic interventions. Current research confirms that repetitive task-specific practice can

significantly improve motor function in pediatric patients. The reason we are doing this research is to find out if there is a possibility to influence the selective voluntary movements in the lower extremities (legs) in children with CP after an intensive rehabilitation program with device called Lokomat.

Type of Research Intervention

This research will involve attendance in intensive rehabilitation program that would take 1 month as well as 1 follow-up visit to the University Rehabilitation Institute of Republic Slovenia, Children's Department of Rehabilitation.

Participant selection

We have invited all children participants from 5 to 15 years old with bilateral spastic cerebral palsy to attend our research study.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. You may change your mind later and stop participating even if you agreed earlier.

Duration

The research takes place in Children's Rehabilitation Department in University Rehabilitation Institute of Republic Slovenia. The research takes over 1 month. During that time, it will be necessary for you to come with a child to the clinic for 5x

per week (20 times) for 1 hour of therapy. We would like to meet with you after few months for a final check-up. We call this "follow-up".

In total, you will be asked to come 23 times (3 pre and after measurements including follow-up, 20 therapy sessions).

Procedures and Protocol

During the research :

- In the first visit functional physiotherapy tests and clinical gait analysis will be assessed.The results will be scored in the core-sheets or in the computer. We call this as "pre-assessment".

- At the next visit, the rehabilitation program with Lokomat device will start.

- You attend rehabilitation program with Lokomat device daily for 4 weeks (20 sessions)

- After 4 weeks, your last session will be completed with all assessments made in the first visit. We call this as "after-assessment".

Side Effects and risks

The Ethics Committee has approved the research study. Chief investigator guarantees that all methods used in the research are non-invasive and will not cause any harm to the patient nor expert.

Benefits

In this research, nor the patient nor the chief investigator will require any money ward, nor anyone will charge you.

Reimbursements

You will not be given any money or gifts to take part in this research.

Confidentiality

The information that we collect from this research project will be kept confidential. Chief investigator guarantees that all personal data, ID and face of the subject will certainly not be presented in the public.

Sharing the results

Confidential information will not be shared. We will publish the results in order that other interested people may learn from our research. On your personal request you may see the results and be fully informed about the results.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact the chief investigator via email : draganazarkovic.physiotherapy@seznam.cz.

Certificate of Consent

I state that I have read foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate in this research. In the case of children's participants (under 18 years old participant), their parents or guardians are signed in this certificate of consent.

Print Name of Participant _____

Date of birth _____

Signature of Participant (parents or guardian) _____

Date _____

        Day/month/year

Print Name of Researcher/person taking the consent : Dragana Žarković, M.Sc.

Signature of Researcher /person taking the

consent_____

Date _____

        Day/month/year

A copy of this ICF has been provided to the participant.

Univerzitetni rehabilitacijski inštitut
*Republike Slovenije - **Soča***

Strinjam se z uporabo fotografij in video posnetkov v raziskovalne namene. Vodja raziskave- Dragana Žarković, M. Sc., zagotavlja varnost osebnih podatkov ter zakrit obraz sodelujočih (le ta bo viden samo v zasebni uporabi).

V Ljubljani _____

Podpis staršev _____

Podpis vodje raziskave _____

Predlog obrazca za sodelujoče

Podpisani

_____

izjavljam, da sem seznanjen z namenom in potekom raziskave, z možnimi koristmi in tveganji.

Seznanjen sem, da lahko na svojo željo brez posledic kadarkoli prekinem sodelovanje. V primeru nujnosti v zvezi z raziskavo lahko pokličem odgovornega nosilca na tel. številko _____ ali dežurnega zdravnika URI-Soča na tel. št. 031 514 076.

Na podlagi danih informacij zavestno pristopam k raziskavi in se zavezujem, da bom vestno upošteval navodila.

Datum:_____

Podpis: _____