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Robotic Neurorehabilitation:

Robot-assisted Gait Training within a multidisciplinary rehabilitation program.

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To almighty God **“Jesus Christ”** for his infinite grace towards me.

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ABSTRACT

New evidence in neuroscience has led to substantial innovations in the provision of rehabilitation therapy, which includes new therapeutic possibilities for patients suffering from central nervous system lesions. The goal of my dissertation is to understand the role of Robot-assisted Gait Training (RAGT) within a multidisciplinary rehabilitation program for patients suffering from outcomes of central nervous system lesions. In this dissertation, I studied participants with traumatic brain Injury (TBI) to determine how cognitive function at admission can interfere in functional improvement after RAGT training in a rehabilitation program and the impact of gender, age and RAGT dose (sessions) on functional improvement in subacute stroke patients.

In my first experiment, I studied a cohort of patients with severe traumatic brain injury (n=80) to investigate the impact of the cognitive level at admission on recovery after RAGT within a multidisciplinary rehabilitation setting. I found evidence that patients with a low cognitive level at admission were mainly in the subacute phase of rehabilitation. Cognitive impairment did not preclude recovery so that irrespective of the level of cognition, patients might benefit from RAGT during a multidisciplinary program. Also, although other heterogeneous factors (age, rehabilitation phase, severity) may have influenced recovery, the cognitive level at admission influence the rehabilitation length of stay (LOS) and the time needed to receive RAGT during the multidisciplinary rehabilitation programme.

In the second set of study in this dissertation, I analyzed a cohort of subacute stroke patients (n= 236) who underwent RAGT in rehabilitation programs to determine the gender-related response.

This approach allowed me to highlight that both genders can be subject to the same standards of treatment beyond the differences in anatomical morphology. While I expected to have a

difference in recovery, instead, I found a significant positive correlation in clinical outcome. Among subacute stroke patients, equal adherence and benefits were observed following RAGT training in both genders. A conventional rehabilitation treatment empowered by RAGT ensured good results in terms of gait recovery, without any gender differences for all parameters considered.

In the third set of this thesis, I studied a subacute stroke population who were undergoing RAGT training during multidisciplinary rehabilitation (n= 236). The principal aim was to investigate the intensity of RAGT (dose) needed to reach the minimal clinical important difference (MCID), measured with the Functional Independence Measure (FIM) and the Functional Ambulatory Category (FAC). Also evaluate the clinical, demographic and functional characteristics that can predict a good functional recovery.

I found, with a regression model, that a significant number of patients achieved MCID with more than 14 sessions. Also, the independence of walking on discharge was influenced by the patient's age and the severity of the damage on admission.

Riassunto

Nuove evidenze nel campo delle neuroscienze hanno portato innovazioni sostanziali in neuroriabilitazione che includono nuove possibilità terapeutiche per i pazienti che soffrono di esiti di lesioni del sistema nervoso centrale. L'obiettivo della mia ricerca è stato di comprendere il ruolo della rieducazione robot-assistita del cammino(RAGT) all'interno di un programma di riabilitazione multidisciplinare per pazienti affetti da esiti di lesioni del sistema nervoso centrale. In questa dissertazione, ho studiato partecipanti con lesioni cerebrali traumatiche (TBI) per determinare in che modo la funzione cognitiva al momento del ricovero può interferire nel miglioramento funzionale dopo RAGT in un programma di riabilitazione. Ho valutato inoltre l'impatto del RAGT su sesso, età e come la dose (sessioni) potrebbe contribuire nel miglioramento funzionale per i pazienti in fase subacuta dell'ictus.

Nella mia prima serie di analisi, ho studiato una coorte di pazienti con grave trauma cranico (TBI) per indagare l'impatto del RAGT a secondo del livello cognitivo al momento del ricovero sul recupero, all'interno di un contesto riabilitativo multidisciplinare. Ho concluso e che i pazienti con un basso livello cognitivo al momento del ricovero erano per lo più nella fase subacuta della riabilitazione e che il deterioramento cognitivo non precludeva il recupero in modo che, indipendentemente dal livello di cognizione, i pazienti potessero beneficiare di RAGT durante un programma multidisciplinare ed ottenere risultati soddisfacenti. Inoltre, sebbene altri fattori eterogenei (età, fase di riabilitazione) possano avere influenzato il recupero; il livello cognitivo ha influenzato la durata della riabilitazione (LOS) e il tempo necessario per ricevere RAGT durante il programma di riabilitazione multidisciplinare.

Nella seconda serie di analisi in questa dissertazione, ho utilizzato il set di dati di una coorte di pazienti con ictus subacuto sottoposti a RAGT nel programma di riabilitazione per determinare la risposta correlata al genere. Questo approccio mi ha permesso di evidenziare che al di là delle differenze di morfologia anatomica, entrambi i sessi possono essere soggetti agli stessi criteri di trattamento. Mentre mi aspettavo di avere differenze nel recupero, invece ho trovato una significativa correlazione positiva nel risultato clinico. Tra i pazienti con ictus subacuto sono stati osservati uguale aderenza e benefici dopo RAGT in entrambi i sessi. Un trattamento riabilitativo convenzionale potenziato da RAGT ha assicurato buoni risultati in termini di recupero dell'andatura, senza differenze di genere per tutti i parametri considerati.

Nella terza serie di questo studio, ho utilizzato una popolazione di ictus subacuto che ha ricevuto RAGT durante la riabilitazione multidisciplinare. Lo scopo principale è stato quello di indagare l'intensità di RAGT (dose) necessaria per il raggiungimento della minima differenza clinica importante (MCID), misurata con la Functional Independence Measure (FIM) e la Functional Ambulatory Category (FAC). Inoltre valutare quali sono le caratteristiche cliniche, demografiche e funzionali che possono predire un buon recupero funzionale. Ho scoperto che un numero significativo di pazienti ha raggiunto la MCID con almeno 14 sessioni. Inoltre, l'indipendenza nel cammino alla dimissione è influenzata dall'età del paziente e dalla gravità del danno al momento del ricovero.

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LIST OF ABBREVIATIONS

BWSTT:	Body Weight Support Training on a Treadmill
CIMT:	Constrained-induced movement therapy
CNS:	Central Nervous System
CT:	Computed Tomography
FAC:	Functional Ambulatory Category
FIM:	Functional Independence Measure
GCS:	Glasgow Coma Scale
GFAP:	Glial Fibrillary Acid Protein
GOS:	Glasgow Outcome Scale
GOSE:	Glasgow Outcome Scale Extended
GR:	Good Responders
ICF:	International Classification Function
LCF:	Level Cognitive Function
LOS:	Length of Stay
MCID:	Minimal Clinical Importance Difference
MNS :	Motor Nervous System
MRI:	Magnetic Resonance Imaging
NS:	Nervous System

OR:	Odd Ratio
PNS:	Peripheral Nervous System
POA:	Paraosteoarthropathy
PR:	Poor Responders
QWA:	Quantitative Walking Analysis
RAGT:	Robot Assist Gait Training
SNS :	Sensory Nervous System
TBI:	Traumatic Brain Injury
WHO:	World Health Organization

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1. INTRODUCTION

Theoretical Background.

Neurorehabilitation definition

A neurological disease is not preventable unless it is congenital or largely hereditary. In life and unexpectedly, one can become a victim to accidents leading to traumatic CNS injuries, strokes, brain tumours and incurable diseases. A sudden event of this kind drastically changes the victim's quality of life and forces him/her to an involuntary total or partial loss of body control and memory capacity. Neurorehabilitation refers to rehabilitation following damage observed or after-effects due to pathologies and/or trauma associated with the nervous system; the nervous system (NS) is one of the most diffuse structures in the body through nerves that are inseparable from mobile organs and cells. It embodies the centre of convergence and divergence, thus conditioning the functioning of several functioning and, more particularly, the entire muscular system (National Research Council 1989). Human Nervous System: convergence and divergence thus conditioning the functioning of several organs of the body and more particularly the entire muscular system).

By this effect, neurorehabilitation encompasses a wide range of motor, cognitive, behavioural, relational disabilities with significant economic consequences. Rehabilitation is restoring an ability lost following a traumatic event or a vascular injury; this restitution can be partial or total. Rehabilitation of behaviors and lost abilities is achieved through exercises and by observing predefined therapeutic norms depending on the severity of the cases (Pernia e al. 2020; Huang et al. 2009). Rehabilitating an injured patient means teaching him/her to capitalize on his/her residual capacities to a maximum extent to compensate for motor, cognitive and behavioural deficits. To do this, the process can be associated with sensory-motor stimulation and, if necessary, with the use of external biomechanical supports for the musculoskeletal system (orthoses, prostheses).

The objective of the initiative is coherent; it consists in having valuable tools to contribute to the improvement of the patient's life quality, by personalizing the rehabilitation plan, by trying to make him/her aware of good behaviours and gestures as well as hygiene rules to be followed even after his/her return home. In other words, the quantification and qualification of neurorehabilitation care focus on physical independence (walking, taking care of oneself without the help of a physical presence) and cognitive independence (making personal decisions, having all these moral senses, and a pleasant mood).

Genesis of Neurorehabilitation

Knowledge and research on the brain are being examined from a scientific perspective; it has long been the focus of attention in the medical profession and is presented as a slow, dynamic experimental field with unclear conclusions. Despite the reticence and obstacles encountered, we have moved from more or less demonstrative empirical positions that are more or less explanatory but accepted by scientific evidence whose veracity is often questioned over time. With research focused on improving well-being, nerve cells' regeneration remains at the heart of the central nervous system's study (CNS). Neurological rehabilitation took off at the end of the 19th century with Joseph Altman and Gopal D's work in 1965, when a hypothesis of probable neuronal regeneration took place. At the beginning of the 20th century, the pathologies and traumas of the CNS were on the increase, none of hereditary origin and generally of unknown aetiology, and other traumas with increasingly disabling after-effects on various parts of the body. This is the reason why research has been stimulated towards solutions to the scourge of CNS cell degeneration. In the mid-20th century and precisely since

2000, ambitious principles within the framework of the brain-injured patient's well being are emphasized by goals aimed at achieving active movement, gait training for patients with paretic limitations, and the need for independence in basic daily living activities (Barrett et al. 2013).

Neurorehabilitation: story and evolution

The delay observed in neurorehabilitation results from static theory on the issue of neuron regeneration; approach resulting from the work of the doctor and researcher Santiago Raymond Cajal during the mid-20th century, which advocates the non-regeneration of nerve cells (Santiago Ramon Y Cajal, 1928). The theories and visions of Cajal and al. froze the search for nearly half a century. Thanks to Joseph Altman et al. 1965's works, a hypothesis of probable neuron regeneration has taken place. Later, the experiment will further extend demonstrating an actual cell replication process at the level of the dentate gyrus and the olfactory bulb into mice by Kaplan. An additional, more precise confirmation of a possibility of cellular replication in some parts of the brain of mice.

The analysis of the works done on birds has demonstrated behaviour, adaptation, and neurons' differentiation by certain auditory and behavioural phenomena. In birds, adult cortex neurons, the hypothesis of a possible replication of the adult cortex neurons has been confirmed (F Nottebohm et al. 1984). These works led to the idea that the new neurons could occur and recombine according to a learning process and growth. In the same footsteps as Ferdinand Nottebohm, A. Beau Alward et al. 2013 have studied canary and have tried to prove that the sound (tone and volume) of the canary is a phenomenon of neurological. This would mean that there would probably be development, replication or differentiation of pre-existing neurons. This instinctive transition from the canary to the mature state of singing will give room to think of a phenomenon of apoptosis (cerebral neuron programmed death) and a cerebral neurons substitution obvious immediate (Alwards Beau 2013). Studies done only on birds and mice will limit this evolutionary trend; after experiments in primates whose species has after experiments in primates whose species have an anatomical and sometimes physiological morphology close to humans, no obvious neuronal replication is observed (Pasko Rakic 1985). However, Pasko RAKIC (1988) further pursuing its primate experiments and using not only [3H] -Thymidine exceptionally used in previous experiences but also glial markers [GFAP] (Glial Fibrillary Acid Protein). The finding will be a presence of stem cells in the cerebral ventricles, spreading to different areas of the brain. Therefore, there would probably be a set of genes controlling ventricular cell production. Understanding the compression of adult stem cells will be deepened by in vitro culture using mice, an experimental specimen easily accessible without strict ethical restriction (Alward et al. 2013; Golmohammadi 2008). It will be observed that adult stem cells of mice have the capacity to differentiate by their continuous growth (taking forms four times larger than their original form). Although it was limited to mice, the experiment helped one understand that adult stem cells could replace needs previously attributed only to foetal stem cells.

This discovery will stimulate experiments in vitro of stem cells adult of primate (Rakíc in 1999) and human stem adult cells with satisfactory results. However, transplants could only be performed on mice. These experiments could not be applied in vivo for primate and specifically on human beings due to the likely toxic sequelae of the replication promoting products (BrdU, 3H) and environmental conditions. The great hope in researching the process on neuroregeneration without the effective perspective of application in the human brain.

Brain Neuroplasticity

Plasticity is an essential characteristic of the nervous system; it implies a natural developmental process favourably produced by knowledge and experiences (both positive and negative) using the concepts of substitution, functional reorganization, and functional flexibility (Shaw et al. 2001). Indeed, nervous system's capacity to change, modulate, reorganize itself according to the residual capacities and experiences lived by the subject, and the ability to compensate for an injury (Robertson et al 1999). Depending on the external stimuli and re-education techniques, the brain has a capacity to reorganize its synaptic networks following a trauma. It is maximum during our young age but is continuous. Therefore, stimulation may be necessary and essential after brain injury and in response to therapeutic intervention in this process, the motor system quickly reacquires an ability to mobilize inactive regions.

Using animal and human models, evidence of modulation of the human brain has been established. All forms of external stimulation (physical exercise, electrical stimulation, environmental impact and daily life activities) are indirectly involved in the brain's internal self-regulation process that drives signals, leading to physiological and anatomical changes (Kleim JA et al 2014). At the basis of the evolution of neurogenesis, it is necessary to understand the complex process known as neuronal plasticity, which is an adaptation process consisting of the reorganization of existing neuronal connections to restore altered cognitive or behavioural functions. This does not fully reflect the plasticity process, although it contributes to functional recovery. In brain damage and injury, it is crucial to consider the axonal regeneration process's limitations and the relatively low levels of plasticity not established (Fawcett 2009). Therefore, it is necessary to know how to dissociate the reorganization of residual brain cells for cognitive and behavioral purposes from cell regeneration. In short, cerebral plasticity is based on all these functional recovery parameters (Rakic 1999). A good evaluation of the type of brain injury and the patient's age at the time of injury are the essential elements of a probable prediction of recovery. Several types of research are currently going in this direction, and many discoveries are still to be made in this field. In biology, plasticity covers many cellular phenomena that occur at very different anatomical levels and on very different time scales. Recovery is a function of the type of lesion and its severity. It can be done in a short time (spontaneous recovery) at the beginning of the rehabilitation process or in a long time (induced recovery), depending on the severity of the lesions, the area concerned and the age of the patient (Fawcett 2009) Indeed, learning is based on neurons' ability to modify their synaptic transmission. It is therefore the connections between neurons that are strengthened. How experiences and practices play a role in increasing synaptic strength and cortical topography changes is now well established (Pascual-Leone et al. 1995; Straudi et al. 2016).

However, the formulation of clinical recommendations for the practice of rehabilitation following brain injury is necessary. Training, which is the practical form of induction of stimuli generating the action of reorganizing the brain's nerve connections, should be precisely targeted and repetitive in circuits affecting well-defined motor maps; this would avoid nerve simulations of unnecessary circuits (Robertson et al 1999; Swain RA et al. 2003). Any motor movement resulting from an intensively repeated sensory impulse brings new information to the NS, which re-establishes connections between the motor centres and the sensory pathways. To this effect, it is established that repeated training and specific exercises with sufficient intensity and well distributed would promote cortical and subcortical reorganization in brain-injured patients (Nudo et al. 1996; Swaim 2003). For this reason, the rehabilitation process requires a multidisciplinary approach with combinations of endurance exercises and multiple skills with varied treatment approaches and well distributed in time and space.

The brain is highly plastic, and that plasticity represents evolution's invention to enable the nervous system to escape the restrictions of its genome (and its highly specialized cellular specification) and adapt to rapidly shifting and often unpredictable environmental and experiential changes. Plastic changes may not necessarily represent a behavioral gain for a given subject. Instead, plasticity may be as much a cause of pathology and disease as it is the substrate for skill acquisition, learning, environmental adaptation, and recovery from insult. Plasticity is not an occasional state of the nervous system but is the nervous system's normal ongoing state throughout the lifespan.

Multidisciplinary Rehabilitation

The nervous system is the most widespread system in the body and interacts with almost every organ and tissue in the body. Independence and better living conditions is the entire scope to reach among these treatments defined as conventional rehabilitation. The program considers each patient's specificities relating to their disability and levels of affection (motor, trouble of consciousness, deficit of language, etc...) and for these circumstances, different professional qualifications are needed (occupational therapy, physical motor rehabilitation, speech therapy and cognitive).

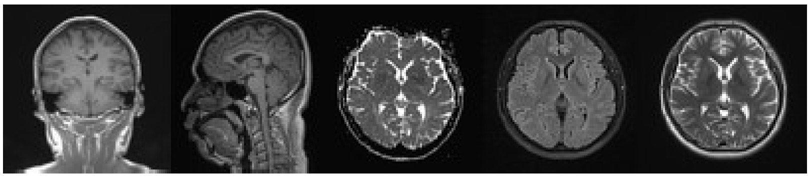
This study's specificity is to associate RAGT in rehabilitation for each patient with the objectives of gait recovery and autonomy in life activities. Reason for organizing the rehabilitation process by defining the temporal windows of training for optimization of recovery. Defining a specific program according to the framework of the international classification of functions (ICF) of the World Health Organization (WHO) is the goal (Lexell et al.2015). Multidisciplinary can be exercised individually or collectively; with objectives and specificities well-targeted for each patient. However, RAGT training is comon for each patient; at admission in rehabilitation, a specific program is determined according to the WHO international classification of functions. At discharge, a clinical evaluation must be made.

Neuroimaging and neurophysiology.

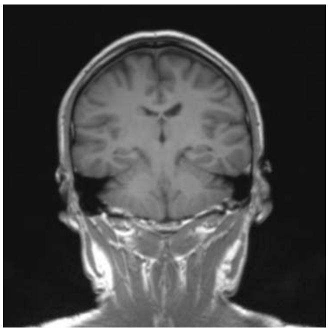
The introduction of medical neuroimaging will bring more precision in clinical diagnostic; that facilitated the better understanding to the process of brain neurophysiology. From the 1980s neuroimaging onwards allows a clear differentiation of brain areas and consequently of neurons damaged from trauma or brain pathology (Wilde et al. 2012; Seitz 2010). Thus, it becomes possible to understand brain neurophysiology and consequently to predict rehabilitation outcomes, monitor in vivo and adjust specific personalized neuroimaging and neurophysiology techniques as needed (TMS, fMRI, EEG, fNIRS), and observe the behaviour of functional and structural hemodynamic factors that influence recovery (Seitz 2010; Mountz 2007).

Figure 1: Representation of normal intracranial appearances.

Coronal T1 Sagittal T1 Axial ADC Axial Flair AxialT2



MRI



Coronal T1

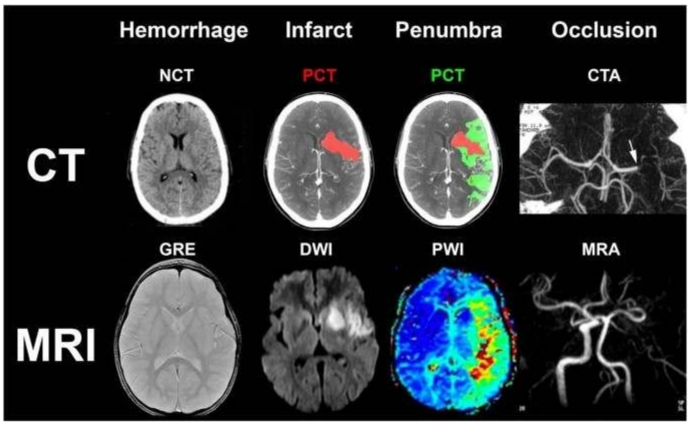
The whole 'sha-bang' of non-contrasted sequences for an MRI brain.

Normal intracranial appearances.

https://radiopaedia.org/cases/normal-mri-brain-adult.

Therefore, the non-invasive tomography method is widely used in the clinical diagnostic system (Maas et al. 2007; Kemp 2000). However, despite the synthetic approach of the image representation, there are still some shortcomings, such as the lack of precision on the location of lesions, their size and position. The introduction of MRI will complement this deficiency (Medical Advisory secretary 2006; Kemp 2000).

Figure 2: CT and MRI representation



(Shams M et al. 2020) https://images.app.goo.gl/Y2xUMC2fhahovx7T6

GAIT Training

To date, neurorehabilitation has remained a constantly evolving challenge and the subject of questioning for human beings. The introduction of new therapies and tools in neuroscience offer hope for people with central nervous system damage. (Warraich et al. 2010). Internal self-regulation that generates physiological and anatomical changes is the consequence (Kleim et al. 2004; Nudo et al. 1996). Functional recovery after CNS injury is supported by exercise and rehabilitation interventions. However, the paradigms defined above are still not well defined; the dose and exercise modalities are not established.

In patients survivors of traumatic brain accident or brain neuropathologies, the mobility is often limited by the walking impairment (Taveggia et al. 2016; Eng JJ et al. 2007) and restoration of walking ability and gait rehabilitation is highly relevant objectives of the rehabilitation process (Bohannon et al. 1991).

Gait analysis

Gait analysis is a growing field of interest to clinicians. It is an effective tool for assessing patient ability, detecting abnormalities in hemiparetic patients (loss of motor strength or selective alteration of motor deficit) and also for rehabilitation of patients who have lost normal gait or have gait disorders. It is therefore no coincidence that walking is one of the most studied forms of biomechanical movement. Its study and understanding presuppose three fields of research:

- Movement of the body with the articular amplitudes.
- The constraints of support on the ground.
- Spatial-temporal parameters such as speed, pace, length and step symmetry.

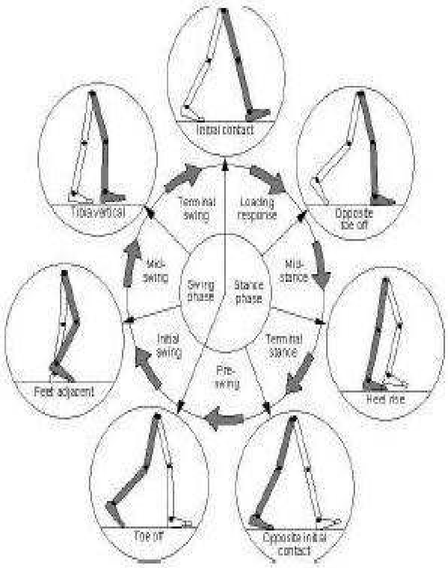
Walking can be defined as a displacement consisting of a translation of the whole body, following articular rotational movements (Kuo et al. 2010). It uses a repetition of body segment sequences to move the body forward while maintaining balance (Shin-Min et al. 1987).

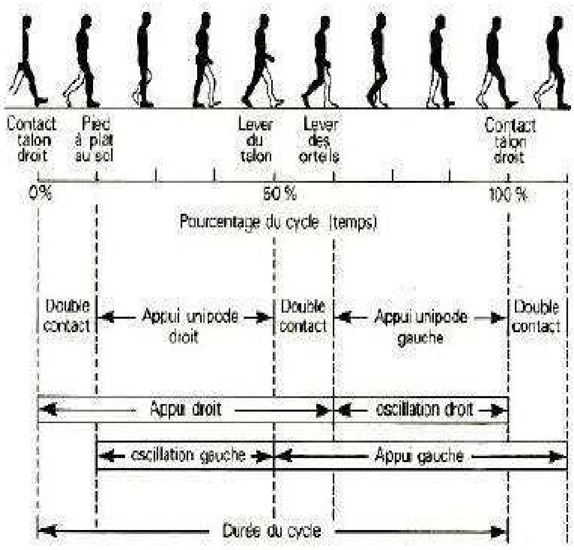
Technological evolution and modernity have led walking laboratories to delineate walking movement phases using a technique known as quantitative walking analysis (QWA). This clinical evaluation tool allows a better discernment and understanding of the anomalies encountered and to adapt treatments (Kay et al. 2000; Bogard et al. 1981). Walking is made up of repetitive cycles, and each cycle is normalized and symmetrically comprises two consecutive steps performed by each of the lower limbs (left-right) (Perry. 1992). For a good analysis and thorough reading, the division into cycles is indicated.

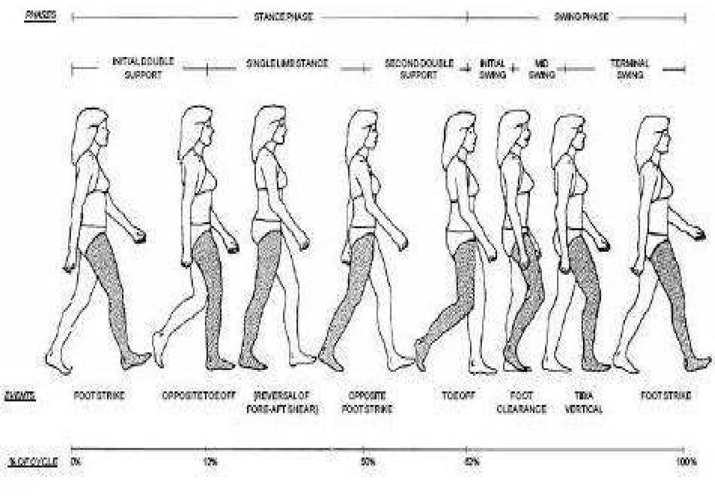
1.4.2. Gait Cycle

The gait cycle consists of several critical elements performed by each of the lower limbs. Usually, it is the contact of one foot on the ground until the same event occurs (for example, the left fooleft foot's full contact on the ground until the next contact of the same foot). It is true that in the normal gait process, the heel should, in principle, first come into contact with the ground. In some cases, pathologies such as digitigrades gait are observed in which the toes make contact with the ground of the feet make the contact with the ground of the feet; hence the importance of considering that the full contact of the foot represents 0% (beginning of the cycle) and that the contact of the same foot represents 100% (end of cycle). The gait cycle can also be broken down into two steps, each step corresponding to 2 main phases; the supporting phase and the oscillating phase, which alternates for each limb during the gait. The support phase lasts about 60% of the cycle, and the oscillating phase about 40% of the cycle for each of the lower limbs (Carollo et al. 2002; Troje 2002). While both limbs are resting on the ground, it is called bipodal or double support; when one of the two limbs is in the support phase, and the other is in the oscillating phase, it is called unipodal support (Troje 2002) (figure3).

Figure 3: Gait cycle representation







Gait cycle representations according to a) Whittle (2002), b) Viel (2000), and c) Viel (2000).c) Sutherland (1994).

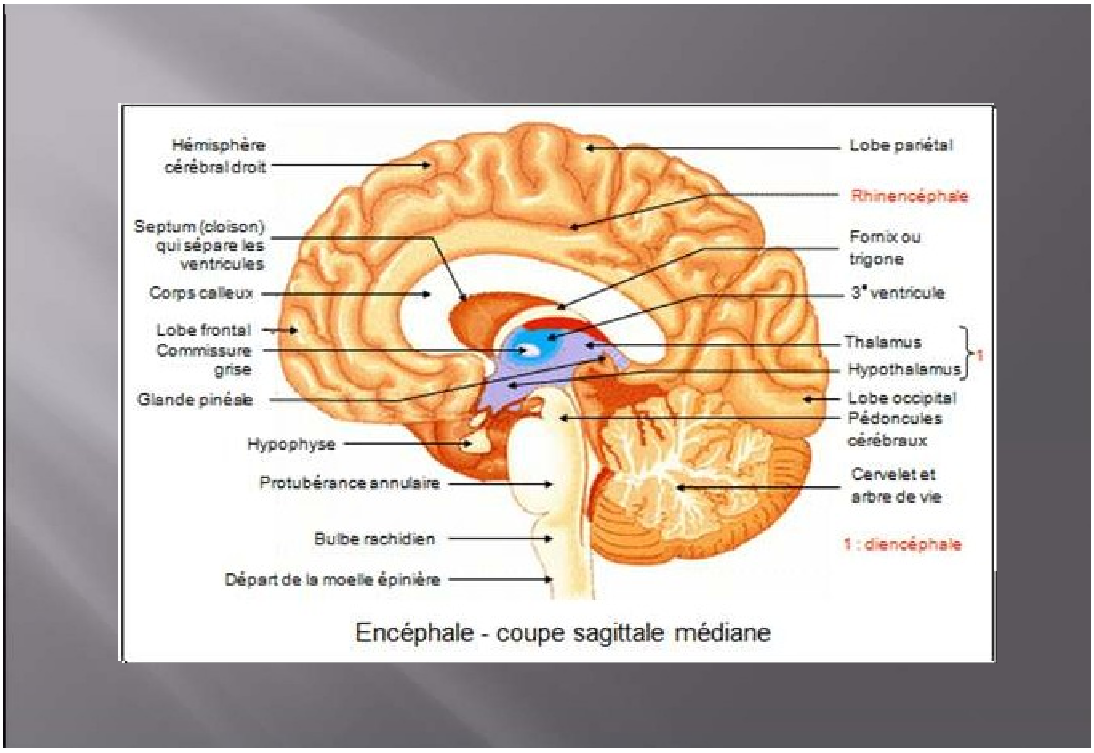
Gait and Neurorehabilitation

Movement Neurophysiology

Physiological movements are coordinated by the nervous system, which is a complex biological structure consisting of the Central Nervous System (CNS) and the Peripheral Nervous System (PNS).

The CNS itself is composed of the brain (brain and cerebellum) and the spinal cord (SP). In this structural organization of the CNS, the brain can be equated to the upper level of movement control and the spinal cord to the lower level. Specific movements are generated in the spinal cord only (case of the reflex arc observed in some decerebrate animals). Other movements, on the other hand, are modulated by the upper level.

Figure 4: CNS: Median sagittal section

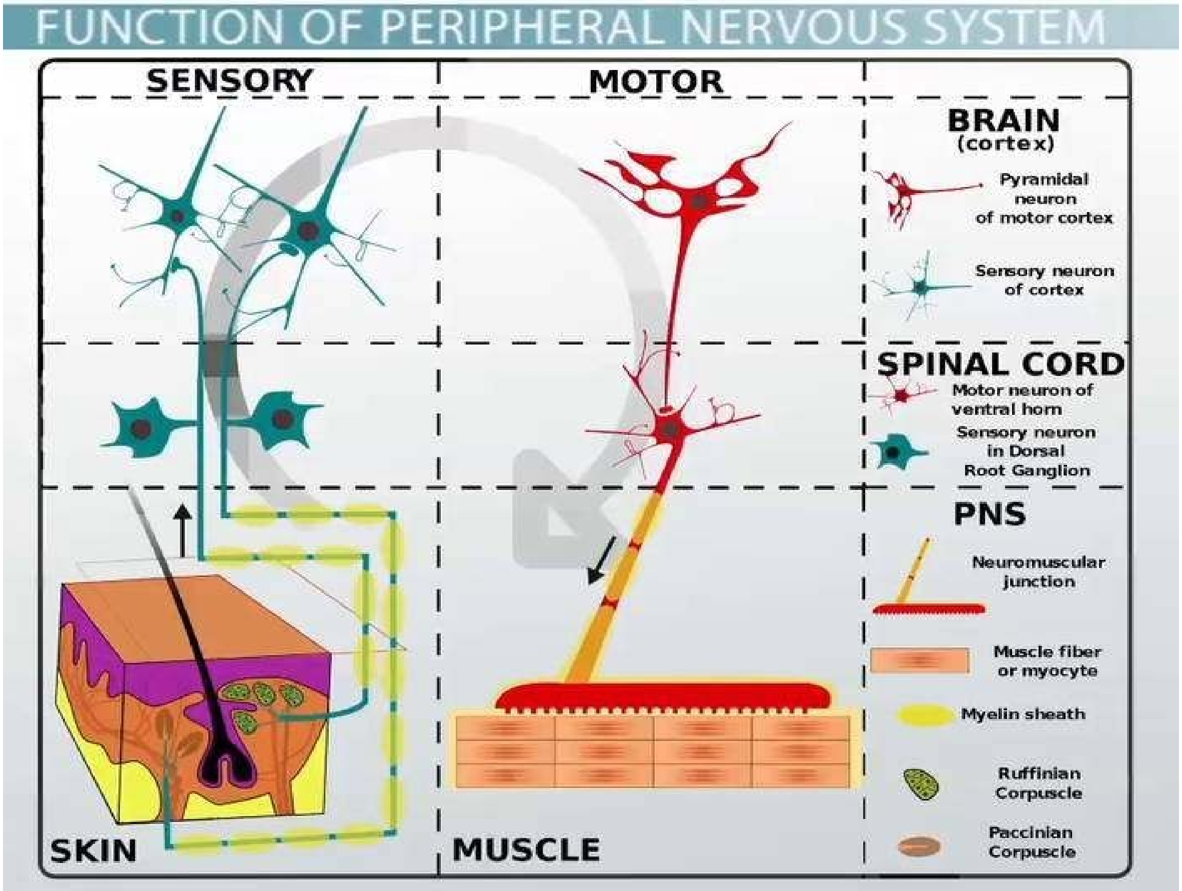


Peripheral Nervous System (PNS)

The PNS is made up of a set of nerves attached to the central nervous system: afferent nerves (sensory nerves) coming from peripheral receptors responsible for perceiving sensations (mechanical, thermal, painful, chemical, etc.), effectors nerves (motor nerves) responsible for controlling peripheral receptors, including muscles. The PNS consists of two sub-systems:

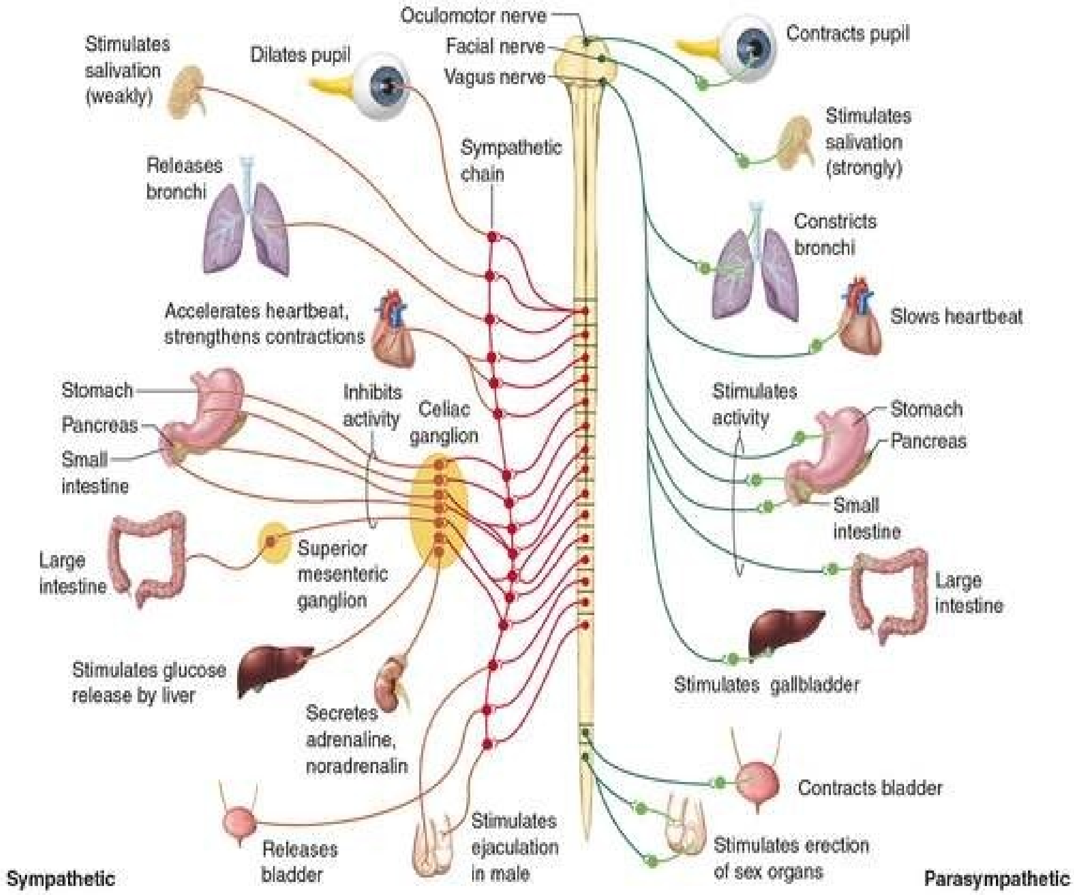
- The vegetative nervous system (autonomous or visceral nervous system) regulates the automatic functions of the body (digestion, breathing, the heart and its activities ...).
- The Somatic Nervous System (SNS); which is responsible for voluntary and involuntary movements as well as sensations; corresponds to both the Motor Nervous System (MNS) and the Sensory Nervous System (SNS). (Figure. 5)

Figure 5: Function of peripheral Nervous System



Movement and walking rehabilitation are based on the SNS and SNM, i.e. the sensory perception of movement, which responds to the stimulus received. It is the system operated by robotics that capitalizes on external (sensory) stimulation through physical and visual exercises to optimize the adaptation of brain-injured patients to walking and specific mobility tasks for a return to activities of daily living.

Figure 6: Human Nervous System: convergence and divergence thus conditioning the functioning of several organs of the body and more particularly the entire muscular system.



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.neurosurgical.

New Technologies and Interventions in Neurorehabilitation.

New technologies are perfectly conceived to improve the development of complex learning, and to this end, neurorehabitation is the basis of many expectations. The first is to develop an understanding of the ingredients to be included in training programs to promote generalized learning. Studies based on neural stimulation, patient motivation and reward processing show promise in this regard.

Second, while the type of improvement desired is usually clear, such as when educators or rehabilitation therapists state their goals for a patient, identifying the cognitive component of a training program to achieve these goals is not always that simple.

Gait studies in animals have proven effective; the system advocates repeated and prolonged training to activate the automatic gaiting by a central pattern generator (De Leons RD et al. 1998; Levely RGE et al. 1986). An essential avenue of scientific exploration experimentally successful in animals, although the fact remains a challenge in humans (Duysens et al. 1986).

Constrained-induced movement therapy (CIMT) is a new therapeutic approach that offers great potential for neurorehabilitation. However, functional recovery improvement would be more effective through non-invasive brain stimulation associated with (CIMT) (Liew SL et al. 2014). Neuronal plasticity has become an interesting phenomenon for the robotics; it is based on learning mechanisms that pave the way to better understand the adaptation phenomena of injured brain patients. These categories of interventions and techniques based on the principles of activity-dependent neuroplasticity and motor recovery mechanisms after CNS injuries are emerging as potential tools to increase functional recovery (Warraich and Kleim 2010). However, well-established evidence from large-scale clinical trials on the effectiveness of these interventions is still lacking, and further research is essential to draw definite conclusions.

Robotics in Neurorehabilitation

In recent years, the introduction of robotics showed interesting rehabilitative outcomes for CNS survivors (Van Peppen et al. 2004; Mehrholz J et al. 2017), offering an alternative to conventional rehabilitation (Laffont et al. 2014). Robotic rehabilitation provides intensive, task-oriented, repeated therapy among different phases of rehabilitation (acute, sub-acute and chronic). Robotic devices might assist human movements providing additional guidance (passive, active, assisted) according to cognitive and motor impairments (Veerbeek et al. 2014; Duncan et al. 2011) and personalized work for favouring recovery and the plasticity-dependent response of brain trauma survivors (Cho JE et al. 2018; Wolpert et al. 2011). Also, the robotic system, allowing partial or total body weight bearing, enables the enrolment of non-ambulatory patients (Iosa et al. 2011) and the prevention of falls during the training sessions (Cho JE et al. 2018). During robotic sessions, to monitor online performances and acquire kinematic and patio-temporal parameters (i.e. speed, smoothness) can be recorded to monitor online performances and obtain clinical information on baseline subjects' characteristics. Effectiveness of robotic training was reported on non-ambulatory rather than for ambulatory stroke patients (Bast BA et al. 2007), suggesting that this approach might represent a rehabilitative strategy for targeted populations. Robotic aims in a clinical setting is clearly defined: the robot can offer massed motor practice, high dose of exercise, the numbers of repetitions of tasks needed to induce neuroplastic changes and post-injury recovery. These materials are also designed to train patients in specific motor tasks (i.e. Lokomat for gait training) and potentially contributes to reduce rehabilitation costs or increase profitability by reducing the workload of therapists.

Robotic therapy is that of constraint-induced movement, favourable for the acquisition of new motor skills. However, in chronic stroke, TBI patients and other neurologic diseases studies failed to demonstrate a more favourable impact of electromechanically or technology-assisted gait training on recovery compared to conventional over ground gait training (Wall A et al.2019; Hsu CY et al. 2019) or its effectiveness in combination with physiotherapy to achieve independent autonomy.

Gait Training with Robotics

Robotic-assisted gait training bows out of experiments conducted on cats with complete thoracic spinal cord injury (Philippson, 1905; Sherrington, 1910; Engberg and Lundberg 1962; Engberg and Lundberg, 1969; Grillner , 1975; Grillner and Zangger, 1979; Forssberg et al, 1980; Rossignol et al., 1982; Lovely et al. 1986).

Robots designed for gait training have these two characteristics in common: treadmill use and body weight support. The Bodyweight Support Training on a Treadmill (BWSTT) is one example.

Body weight support Training on a treadmill (BWSTT)

In the beginning, we had Bodyweight Support as a tool for gait training. Later, we realized that we would have to adapt the walking speed according to the patient's voluntary control (Berra et al. 2019). This was when the BWS was combined with the treadmill to form BWSTT (Park HS et al. 2011) (Fig. 7). With this approach, the therapists could treat patients objectively in a more realistic atmosphere and setting. The equipment for BWSTT is composed of a standard treadmill fitted with the weight supporting apparatus (Noramco Fitness and Spino Flex, USA). The patient wears a modified mountain climber’s harness with an adjustable belt around the pelvis and thigh and an adjustable belt above to support their body weight. A therapist assisted with leg propulsion if the patient could not lift his/her paretic leg. At the beginning of training, some subjects need two therapists to guide the pelvis's movement forward and to flex and extend the hemiplegic leg during the swing and stance phases of gait. The initial body weight support was set at 30%~40%. The speed of the treadmill's speed was set at 0.5 mph (miles per hour). The duration of training is defined between 20 to 40 minutes, depending on the patient’s performances. As treatment progress, the body weight support will gradually decrease, and the velocity will gradually increase (Bohannon RW et al. 2013). BWSTT is a high-intensity, task-oriented intervention to restore locomotors functions in people who suffered from CNS lesions (Berra et al. 2019; Robin et al. 2020). However, this training can be highly physically demanding for physical therapists and subjects, especially when subjects with severe gait impairments and markedly reduced mobility are trained (Kwakmanet et al. 2020) (see figure 7). To bypass the limitations of BSWTT to improve motor learning and walking training, new robotic devices inspired by BSWTT will be designed. We currently have in the field of neurorehabilitation walking robots with end effectors and exoskeletons such as the Lokomat (Hocoma Switzerland).

Figure 7: Body Weight Support Training on a treadmill (BWSTT)

Exoskeleton robot as gait instrument training in neurorehabilitation

The most popular exoskeleton device in used i the market is Lokomat; subjects wear a harness attached to a system to provide body weight support and walk on a treadmill. The patient is secured with three cuffs per leg to the orthosis. The hip and knee joint of the device is actuated (Figure 8).

Figure 8. Structure of LOKOMAT (Hocoma Switzerland)

The robotic control uses an adjustable (impedance controller) with adjustable predefined trajectories for hip and knee joints. Elastic straps provide dorsiflexion assistance to the feet. The Lokomat system can be adjusted from 100% to 0%. To get the best possible fit for each patient development include a freed mode, new control mechanisms and innovative virtual scenarios (Hubertus et al. 2018) (see figure 9). The treadmill's speed was set from 0 to approximately 3 km/h, and body weight support ranged from 0% to 100%. As training progressed, adjustments in the guidance, the amount of body weight support and treadmill speed are made according to subject performance. A therapist can use games providing bio-feedback for increasing the patient's motivation. The Lokomat can be considered a humanoid robot enhanced by its stability and balance against falling during physical interaction with humans. This gives it the pre-eminence in gait rehabilitation because the interaction of the human with the ground through the dynamic sensory-motor loop gait movement is rhythmic, synchronized and adapted to the control of the robot (Faugloire et al. 2006). This pre-established dynamic coupling allows both the robot and the lower limbs to generate locomotors rhythms and control posture. Thus, lower limb movement and upper body balance control are coordinated by Lokomat (MC Cra et al. 2008; Cattaert et al. 2001).

Figure 9: Lokomat during gait Training

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Numerous studies in neurorehabilitation in primates have shown substantial functional reorganization after repeated training exercises (Nudo et al. 1996; Kwakkel et al. 1997). The repetition of a particular task would promote cortical and subcortical reorganization of brain-damaged patients. The Lokomat is one of the robotic instruments best suited to the principle of repeated training and optimal with the nursing economy. Patient's participation is active or passive, depending on the degree of damage. The robot accompanies the movement and adapts the task's difficulty to the patient's functional level. The active and progressive sensor-motor (re)learning through repeated and prolonged simulation of the different walking phases nourishes the proprioceptive re-afferences. This sensory-motor learning consists of working on the reorganization, through practice and sensory stimulation, of the spinal and supra-spinal circuits that can be reached during a lesion. This reorganization is built on a constant circuit/loop afference-efference-reference whose principle is based on the idea that any movement brings new information to the nervous system, mainly of a sensory nature.

Therefore, the movement is in synergy with the sensory pathways, thus allowing an optimization of the movement to be performed. By intensive repetition of the same movement, the circuits involved in the realization of locomotor movements will be activated, allowing the nervous system to establish or re-establish connections between the motor centers and the sensory pathways affected to varying degrees depending on the lesion. A brain - robot interface is established during the RAGT. During the rehabilitation process, resulting biomechanical manifestations are evident (reinforcement of the hip flexors, symmetry of the step, control of the support transfer) and walking with a near-normal pattern). However, this strategy, which relies more on motor function, by no means satisfies the expectations of morbid patients and those who cannot engage in active therapy movement.

AIMS OF THE STUDY

This study aims to highlight the impact of Robot-assisted Gait Training within a multidisciplinary rehabilitation program. Several therapeutic approaches have been introduced to facilitate the process of functional and gait recovery. New technologies such as robotic devices have been introduced in a clinical setting (Poli et al., 2013; Bradley et al. 2020; Moon et al. 2017; Brook et al. 1991) with objective better functional outcomes. The development of robot-assisted devices offers great potential for modern neurorehabilitation, based on exercise-related neuroplasticity principles (Moon et al.2017; Warraich et al. 2010). The Lokomat exoskeleton known to the general public in walking rehabilitation allows an intensive and repetitive practice of walking movements reproducing specific articular gestures of the lower limbs (hip, knees, and ankle). Its use has been tested in patients suffering from CNS injuries of different etiologies, such as stroke (Veerbeek 2014; Duncan 2011), brain injuries (Esquenazi 2016).

To this effect,

(1) I investigated the impact of the cognitive level at admission on functional recovery in a cohort of patients with severe TBI who received RAGT training within a multidisciplinary rehabilitation setting.

(2) Considering the known sex differences in occurrence and severity of a stroke, as for therapies (Sohrabji et al.2017), also rehabilitation should consider possible sex differences in treatment. The retrospective study also focuses on presenting the results attained in terms of functional recovery in a cohort of subacute stroke patients who received RAGT during a multidisciplinary rehabilitation program. Specifically, to report females' response to understand the impact of RAGT as possible targeted strategy in stroke rehabilitation.

(3) A question remains to know how the number of RAGT sessions associated with conventional rehabilitation could have an impact on the functional outcome and what could be the influence of parameters of care (length of stay at the hospital and the time elapsed since the stroke to RAGT training), if they are correlated or not with the dose; nothing yet clearly indicates the relationship about this aspect (Mehrholz et al. 2017). Recently, it has been hypothesized how the dose of RAGT training may influence functional recovery in patients who have undergone a multidisciplinary program (Straudi et al. 2020). In this project, we also identify the optimal dose of RAGT that can lead to a favourable outcome in a sample of subacute stroke survivors.

Patients were retrospectively collected within ten years and were assessed before and after RAGT using conventional qualitative and quantitative clinical scales. (FAC, FIM, DRS, GOSE, LCF etc.…).

REFERENCES

Alwards BA, Balthazart J, Ball GF. Differential effects of global versus local testosterone on singing behaviour and it underlying neutral substrate. Proc Natl Acad Sci U S A. 2013; 110(48); 19573-8. Doi: 10.1073/pnas.1311371110.

Bach Y, Rita P. Central nervous system lesions: sprouling and unmasking in rehabilitation. Arch PhysMed Rhabil. 1981: 62(9):413-417. PMID: 6793021.

Barrett AM, Mooyeon Oh-Park, Peii Chen, and Nneka L. Ifejika. Neurol Clin Pract. 2013; 3(6): 484–492.doi: 10.1212/01.CPJ.0000437088.98407.fa

Bast BA, Grenwald BD. Preventing hip fracture after stroke. Top Stroke Rehabil. 2007; 14(4) 67-79. Doi.org/10.1310/tsr1404-67.

Berra E, De Icco R, Avenali M, Dagna C, Cristina S, Pacchetti C, Fresia M, Sandrini G and Tassorelli C. Body Weight Support Combined With Treadmill in the Rehabilitation of Parkinsonian Gait: A Review of Literature and New Data From a Controlled Study. Front. Neurol., 2019. https://doi.org/10.3389/fneur.2018.01066.

Bogard E, Richards CL. Gait analysis and relearning of gait control in hemiplegic patients. Phys Can. 1981; 33: 223- 230.

Bohannon, RH A. W. Andrews, and S. S. Glenney, "Minimal clinically important difference for comfortable speed as a measure of gait performance in patients undergoing inpatient rehabilitation afterstroke," Journal of Physical Therapy Science. 2013; vol. 25, no. 10, pp. 1223–1225,

Bohannon RW, Horton MG, Wikholm JB. Importance of four variables of walking to patients with stroke. Int J Rehabil Res. 1991;14(3):246-50. doi: 10.1097/00004356-199109000-00010. PMID: 1938039).

Carollo JJ, Matthews D. Strategies for clinical motion analysis based on functional decomposition of the gait cycle. Phys Med Rehabil Clin N Am. 2002; 13(4):949-77. DOI: 10.1016/s1047-9651(02)00029-3.

Cattaert D et Leray D. Adaptive motor control in the crayfish. Progress in Neurobiology. 2001; 63: 199 – 240.

Cho JE, Yoo JS, Kim KE, Cho ST, Jang WS, Cho KH, Lee WH. Systematic Review of Appropriate Robotic Intervention for Gait Function in Subacute Stroke Patients. Biomed Res Int. 2018 Feb 6;2018:4085298. doi: 10.1155/2018/4085298. PMID: 29546057; PMCID: PMC5818914).

De Leons RD, Hodgon JA, Roy RR,Edgerton VR. Full weigh-bearing hindlimb standing following sand trainingin adult spial cat. J neurophysiology. 1998; 80(1): 83-91**.**

Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK; LEAPS Investigative Team. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011 May 26;364(21):2026-36. doi: 10.1056/NEJMoa1010790. PMID: 21612471; PMCID: PMC3175688).

Duysens, Van de Crommer HW. Neural control of locomotion ; the central pattern generator from cats to humans. Gait posture 1998; 7 (2): 131-141).

Eng JJ, Tang PF. Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. Expert Rev Neurother. 2007 Oct; 7(10):1417-36. doi: 10.1586/14737175.7.10.1417. PMID: 17939776; PMCID: PMC3196659.

Fawcett J. Molecular control of brain plasticity repair. Progress in Brain research. 2009 ;vol 175 : 501-509. https://doi.org/10.1016/S0079-6123(09)17534-9);

Gaillard F. The whole 'sha-bang' of non-contrasted sequences for an MRI brain. Normal intracranial appearances. https://radiopaedia.org/cases/normal-mri-brain-adult.

Golmohammadi M G, Blackmore DG, Large B, Azari H, Esfandiary E, Paxinos G, Franklin KBJ, Reynolds BA, Rietze RL. Comparative analysis of the frequency and distribution of stem and progenitor cells in the adult mouse brain. Stem Cells. 2008; 26(4): 979-987. https://doi.org/10.1634/stemcells.2007-0919.

Gould E, Reeves AJ, Graziano MSA, Gross CG. Neurogenesis in the Neocortex of Adult Primates J.Neurosci.1999;286(5439):548-552 DOI: 10.1126/science.286.5439.548.

Hsu CY, Cheng YH, Lai CH, Lin YN. Clinical non-superiority of technology-assisted gait training with body weight support in patients with subacute stroke: A meta-analysis. Ann Phys Rehabil Med. 2019 Oct 30:S1877-0657(19)30153-8. doi: 10.1016/j.rehab.2019.09.009. Epub ahead of print. PMID: 31676456)

Huang VS & Krakauer JW. Robotic neurorehabilitation: a computational motor learning perspective. Journal of NeuroEngineering and Rehabilitation. 2009; 6(5). https://doi.org/10.1186/1743-0003-6-5-

Huberus JA Van Hedel, Severini G, Scarton A, O'Brien A, Tamsin Reed, et al. Advanced Robotic therapy integrated Ceters(ARTIC):an international collaboration facilitating the application of reabiliation technologies.

Iosa M, Morone G, Bragoni M, De Angelis D, Venturiero V, Coiro P, Pratesi L, Paolucci S. Driving electromechanically assisted Gait Trainer for people with stroke. J Rehabil Res Dev. 2011;48(2):135-46. doi: 10.1682/jrrd.2010.04.0069. PMID: 21480088).

Kaplan MS , Hinds JW, Neurogenesis in adult rat: electron microscopie analysis of light radioautographs. Science. 1977; 197(4308): 1092-1094. DOI: 10.1126/science.887941.

Kay RM, Denis S, Kethlefsen S, Teynolds RA, Skaggs DL, et Tolo VT. The effectof preoperative gait analysis on orthpopaedic decision making. Clnical Orthopaedic and related research. 2000; 372; pp 217-222.

Kemp GJ: Non-Invasive Methods for Studying Brain Energy Metabolism: What They Show and What It Means. Dev Neurosci 2000; 22:418-428. Doi: 10.1159/000017471

Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M. Cortical synaptogenesis and motor map reorganization occur during late but not early, phase of motor skill learning. J Neurosci. 2004; 24(3): 628-33. Doi: 10.1523/JNEUROSCI.3440-03.2004.

Kuo AD, Donelan JM. Dynamic Principles of Gait and Their Clinical Implications. 2010. Phys Ther; 90(2): 157-174. doi: 10.2522/ptj.20090125.

Kwakman RCH., Sommers J, Horn, J. *et al.* Steps to recovery: body weight-supported treadmill training for critically ill patients: a randomized controlled trial. *Trials* **21,**409 (2020). https://doi.org/10.1186/s13063-020-04333-y

Laffont I, Bakhti K, Coroian F, van Dokkum L, Mottet D, Schweighofer N, Froger J. Innovative technologies applied to sensorimotor rehabilitation after stroke. Ann Phys Rehabil Med. 2014Nov;57(8):543-551. doi: 10.1016/j.rehab.2014.08.007. Epub 2014 Aug 26. PMID: 25261273.

Levely RG, Gregor RJ, Roy RR, Egerton VR, Efets of training o the recovery of full wei-bearing steping n adult spinal cat. Exp Neurol 1986; 92(2): 421-435.

Lexell J & Brogårdh C. The use of ICF in the neurorehabilitation process. NeuroRehabilitation, 2015; 36(1), 5-9. https://doi.org/10.3233/NRE-141184

Liew SL , Santarnecchi E Buch ER, Cohen LG. Non invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. Frnt Hum Neuroscien,2014; 8 :378.

Maas AIR, Steverberg EW, Butcher I, Dammers R, Lu J, Marmarou A, Mushkudiani NA, McHugh GS and Murray GD. Prognostic Value of Computerized Tomography Scan Characteristics in Traumatic Brain Injury: Results from The IMPACT Study.Journal of Neurotrauma. 2007;Vol. 24, No. 2. https://doi.org/10.1089/neu.2006.0033

Maquez C, Tessa H, Hammond FM, Frol A, Hudak A, Harper CR, O'Neil Pirozzi T, Whyte J, Carlile M, and Diaz R. Impact of Age on Long-term Recovery From Traumatic Brain Injury.

Mc Crea DA, Ryback IA. Organisation of mammalian locomoyor rhythm and pattern generation. Brain Research Review. 2008. 57(1): 134-146.

Medical Advisory Secretariat. Functional brain imaging: an evidence-based analysis. Ont Health Technol Assess Ser. 2006;6(22):1-79.

Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke.Cochrane Database Syst Rev. 2013 Jul 25;7:CD006185.

Mehrholz J, Thomas S, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev. 2017; 8(8):CD002840. doi: 10.1002/14651858.CD002840.pub4.PMID: 28815562; PMCID: PMC6483714

Mountz JM. Nuclear medicine in the rehabilitative treatment evaluation in stroke recovery. Role of diaschisis resolution and cerebral reorganization. Eura Medicophys. 2007; 43(2): 221-39.

National Research Council (US) Committee on Research Opportunities in Biology. Opportunities in Biology. Washington (DC). The Nervous System and Behavior. National Academies Press (US). 1989; 6: https://www.ncbi.nlm.nih.gov/books/NBK217810/

Nottebohm F . Birdsong as a model in which to study brain processes related to learning. Condor journal of cooper ornithological society. 1984. 83(3), 221-236).

Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci 1996; 16: 785-807. 1996

Park HS, Yoon JW, Kim J, Iseki K, Hallett M. Development of a VR-based treadmill control interface for gait assessment of patients with Parkinson's disease. IEEE Int Conf Rehabil Robot. (2011) 2011: 5975463. Doi: 10.1109/icorr.2011.5975463).

Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills.J Neurophysiol. 1995; 74(3):1037-45.

Pernia DM. Experiential Neurorehabilitation: A Neurological Therapy Based on the EnactiveParadigm. 2020. Front Psychol. 11: 924. doi: 10.3389/fpsyg.2020.00924.

Perry J, Thorofare KS, Davids JR. Gait analysis normal and pathological function. Journal of Pediatric Orthopaedics.1992; 12(6):815. .

Rakíc P. Limits of neurogenesis in primates.Science.1985;227(4690):1054-6
DOI: 10.1126/science.3975601.

Robertson IH, & Murre J MJ, Rehabilitation of brain damage: Brain plasticity and principles of guided recovery. Psychological Bulletin.1999; *125*(5):544–575. https://doi.org/10.1037/0033-2909.125.5.544).

Sambert JL, Injeyan S,Loisel W, Bindel P, Bébin Y, Le Doze S, et al Rééducation robotisée (Lokomat) ans les lésion médulaire incmplètes et activation du généraeur spinal de la marche. Rev Chir Orthopédique Traumatol. 2010, 96 (4) : 21.30.

Santiago Ramon Y cajal, Argument structural :« In the adult centers, the nerf paths are something fixed, and immuable : everything may die, nothing may be regenerated »1928.

Seitz RJ. How imaging will guide rehabilitation. Curr Opin Neurol. 2010. 23(1): 79-86. Doi:10.1097/WCO.0b013e328334c84d. .

Shams, M., Shams, S. & Wintermark, M. What's new in imaging of acute stroke?. *Intensive CareMed* . 2020; **46,** 1453–1456. https://doi.org/10.1007/s00134-020-06070-x.

Shaw CA & Mc Eacher JC. Toward a theory of neuroplasticity. Philadelphia: Psychology press.2001.

Shin-Min Song, Kenneth J. Waldron. An Analytical Approach for Gait Study and Its Applications on Wave Gaits. Inter journal of robotic research.1987; 6(2). https://doi.org/10.1177/027836498700600205

Sohrabji F, Park MJ, Mahnke AH. Sex differences in stroke therapies. J Neurosci Res. 2017 Jan 2;95(1-2):681-691. doi: 10.1002/jnr.23855. PMID: 27870437; PMCID: PMC5125551..

Straudi S, Manfredini F, Lamberti N, Martinuzzi C, Maietti E, Basaglia N. Robot-assisted gait training is not superior to intensive overground walking in multiple sclerosis with severe disability (the RAGTIME study): A randomized controlled trial. Mult Scler. 2020 May;26(6):716-724. doi: 10.1177/1352458519833901. Epub 2019 Mar 4. PMID: 30829117)

Straudi S et al.Monitoring step activity during task oriented-circuit training in chronic stroke survivors. 2016 ; Ann Rehabil Med. 40(6): 989–997).

Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, et al. Prolonged exercise induces angiogenesis and increases cerebral flood volume in primary motor cortex of the rat. Neuroscience 2003; 117: 1037-1046

Taveggia G, Borboni A, Mulé C, Villafañe JH, Negrini S. Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. Int J Rehabil Res. 2016 Mar;39(1):29-35. doi: 10.1097/MRR.0000000000000137. PMID: 26512928; PMCID: PMC4900426).

Troje N. Decomposing biological motion: A framework for analysis and synthesis of human gait patterns. Journal of Vision. 2002; 2(5):371-87. DOI: 10.1167/2.5.2.

Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004;18(8):833-62. doi: 10.1191/0269215504cr843oa. PMID: 15609840. .

Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014 Feb 4;9(2):e87987. doi: 10.1371/journal.pone.0087987. PMID: 24505342; PMCID: PMC3913786).

Wall A, Borg J, Palmcrantz S. Self-perceived functioning and disability after randomized conventional and electromechanically-assisted gait training in subacute stroke: A 6 months follow-up. NeuroRehabilitation. 2019; 45(4):501-511. Doi: 10.3233/NRE-192929.

Warraich Z, Kleim JA. Neural plasticity: the biological substrate for neurorehabilitation.PM R. 2010; 2(12 Suppl 2):S208-19.

Wilde EA, Huner JV, Bigler ED. Neuroimaging in neurorehabilitation. NeuroRehabilitation. 2012; 31(3): 223-226. Doi: 10.3233/NRE-2012-0792.

Wolpert DM, Diedrichsen J, Flanagan JR. Principles of sensorimotor learning. Nat Rev Neurosci. 2011 Oct 27;12(12):739-51. doi: 10.1038/nrn3112. PMID: 22033537).

2. PUBLISHED AND SUBMITTED PAPERS

2.1 The cognitive level does not interfere with recovery after robot-assisted gait training in Traumatic Brain Injury: A ten year cohort study. Lissom LO, Bonsangue V, Macca M, Severini G, Lavezzi S, Basaglia N, Straudi S. Journal Technology and Disability. 2021. Vol. Pre-press, n° Pre-press, pp 1-7. Doi: 10:3233/TAD-200324.

Abstract

There is still no clear evidence available on the role of robot-assisted gait training (RAGT) as part of a multidisciplinary rehabilitation programme in patients with severe traumatic brain injury (TBI) and on the relationship between this intervention and cognitive impairment.

Aims: This study investigates the impact of cognitive level at admission on functional recovery in a cohort of patients with severe TBI who received RAGT training within a multidisciplinary rehabilitation setting.

Methods: In this observational study, we included patients with gait disturbance due to a severe TBI who undergone an inpatient multidisciplinary rehabilitation at Ferrara University Hospital and received a robot-assisted gait rehabilitation (Lokomat: Hocoma, Switzerland) between January 2007 and December 2017. Participants were grouped into three classes according to their level of cognitive functioning (LCF) at admission (LCF 2-3; LCF 4-5-6; LCF 7-8). We collected demographics (sex, age), clinical data, and a set of outcome measures at admission and discharge.

Results: In this study, we registered 80 patients, 19 females and 61 males, 35.3 ± 14.85 years. The analysis showed that patients with a low cognitive level at admission were mostly in the subacute phase of rehabilitation ($p = 0.001$). Cognitive impairment did not preclude functional recovery after RAGT training in terms of level of cognitive function ($R^2 = 0.68$; $p < 0.0001$), functional independence ($R^2 = 0.30$; $p < 0.0001$) and overall disability ($R^2 = 0.32$; $p < 0.0001$).

Conclusion: Patients with severe TBI might benefit from RAGT during a multidisciplinary program, irrespective of their level of cognition.

Key words: Traumatic brain injury, Robot-assisted gait training, Cognition, Multidisciplinary rehabilitation, Recovery, Exoskeleton, Disability.

INTRODUCTION

Traumatic brain injury (TBI) is a common cause of neurological damage and disability that affects the medical, social and economic spheres. To date, according to recent epidemiological studies, TBI incidence rate in Europe is estimated between 83.3 and 849 per 100.000 of the population per year (regional-level studies) (Brazinova et al.2018).Cognitive impairment is usually also a consequence of brain trauma. In the case of moderate and severe TBIs, statistics indicate cognitive sequelae in approximately 65% of patients, and physical sequelae in 40% of patients. Even in cases of mild TBI without visible physical sequelae, 43% of people suffer from cognitive impairments (Benedictus et al. 2010; Rabinowitz et al. 2014). The parts of the brain that are most commonly affected in traumatic brain injuries are the frontal and temporal lobes (Stuss et al. 2011); the frontal lobe is considered the crucial neural substrate for cognitive and social behaviour. For this reason, assessment of patients following a severe TBI maintains a focus on disorders of consciousness outcomes (Rabinowitz et al. 2014).

Pilot studies have shown that patients with TBI have good cognitive and functional recovery through rehabilitation, especially young patients in the acute phase (Fraser et al.2019). Other studies have shown high correlation between cognitive recovery and functional improvement in these patients (McLafferty et al. 2016; Smania et al. 2013). The past two decades have seen the introduction of new rehabilitation interventions that are based on the use of robotics. RAGT is intended to allow the patient to practice more ‘normal’ gait patterns. Robotic exoskeletons can provide the user with intensive, goal-directed movement repetition and stability and balance during gait, compared to conventional physical therapy. Robot-assisted therapy helps patients to accelerate functional recovery (Nolan 2018 et al.; Esquenazi et al

2012). The use of robotic technology combined with conventional rehabilitation is an added value that not only improves patients' mobility, but also allows health professionals to organise their work better (Delhem 2017; O'Brien 2016; Straudi 2020). Moreover, RAGT can potentially improve the gait pattern and to increase the volume of patients' exercise while relieving the therapist's physical load, and shortening the duration of hospitalization (Equenazi 2017). So far, studies have reported a potential beneficial effect of RAGT in patients with TBI, both in terms of walking function and of gait symmetry (Nolan et al.2014; O'Brien 2016; Esquenazi 2013). Moreover, this intervention seems to be safe and feasible even in patients with severe TBI with disorders of consciousness, with positive effects on cognition.

The main objective of this observational study is to investigate the influence of the cognitive level at admission on a variety of outcomes including disability, walking function, cognitive level, and independence of daily living in a cohort of patients with severe traumatic brain injury who received RAGT within the context of multidisciplinary rehabilitation.

MATERIALS AND METHODS

We retrospectively analysed a database that includes patients with severe TBI admitted to an inpatient multidisciplinary rehabilitation programme of the University of Ferrara and who received robot-assisted gait rehabilitation between January 2007 to December 2017. Ethics committee approved the study, but written informed consent was not collectable from all patients since part of them was no longer attending the rehabilitation clinics.

Subjects

The criteria of inclusion for the study were: i) male or female aged over 18; ii) severe or moderate traumatic brain injury (TBI) according to the Glasgow Coma Scale (GCS) (Teasdale 1974).Patients with medical instability, aggressive behavior and skin lesions were excluded from the use of RAGT. We collected the following demographic and clinical data: age; 2) sex;

3) Glasgow Outcome Scale Extended (GOSE) at admission and discharge; 4) physical limitations (paraosteoarthropathy, limb fractures, spasticity); 5) Level of Cognitive Functioning (LCF) at admission and discharge; 6) motor impairment (right hemiplegia, left hemiplegia, tetraplegia, motor disorders); 7) rehabilitation phase (sub-acute, defined as < 6 months and chronic, defined as > 6 months from the acute event); 8) Functional independence measure (FIM): total score (tFIM), motor subscore (mFIM) and cognitive subscore (cFIM) at admission and discharge;9) Functional Ambulatory Classification (FAC) at admission and discharge. Moreover, a set of measures related to rehabilitation training protocol were collected, including i) the length of stay in the hospital (LOS), ii) the number of RAGT sessions, iii) the period since TBI event and RAGT training

In our analysis, we focused on the impact of the cognitive level at admission measured by the Level of Cognitive Functioning (LCF) score. It is a scale used to classify cognitive and behavioral disorders caused by TBI. It is structured in eight levels, characterizing the level of cognitive damage from a coma to the full recovery of consciousness (Conigan et al. 1997; Smith-Knapp et al.1996). We divided our sample in three main classes according to their LCF level at rehabilitation admission. The first group includes patients with disorders of consciousness that are scored as LCF 2 or 3; the second group is characterized by patients with moderate to severe cognitive and behavioral disorders (LCF score of 4, 5 and 6); the third group presents mild to moderate cognitive and behavioral disorders (LCF score 7 and 8).

Interventions

All patients of the program received robot-assisted gait rehabilitation. RAGT was performed using a robotic exoskeleton system (Lokomat: Hocoma, Switzerland) that can guide hip and knee flexion through braces connecting the patient's legs to the machine. It also provides body weight support (0-100%) through a harness, along with the level of assistance provided by the device. The entire device (including the harness and the motorized exoskeleton orthosis) can be adjusted according to the requirements of the process of treadmill rehabilitation. Motorized exoskeleton orthosis have a biomechanical role, which is to guide movements at the hips and knees that mimic a physiological gait pattern (Riener 2010).Parameters are defined based on the functional characteristics of the patient, starting with a 50% reduction in body weight and 100% of the guidance provided by the robot. Over the sessions, adjustments can be made in increments or decrements of 10%. The RAGT session lasts approximately 45 minutes to an hour, including patient preparation. The treadmill speed can vary from 0.1 to 3 km/h (Artic 2018). In addition to RAGT, patients benefited from a multidisciplinary rehabilitation programme defined according to the individual's needs (conventional motor rehabilitation, occupational therapy, speech therapy and cognitive rehabilitation).

Multidisciplinary rehabilitation

Rehabilitation is the act of restoring health and function of body and mind. For this purpose, specialized care for a variety of deficiencies due TBI help patients to regain their independence and the better living conditions. Among these treatments defined by conventional rehabilitation, we distinguish occupational therapy, speech therapy, physical and manual rehabilitation, psychological therapy. In addition to RAGT, each patient received multidisciplinary rehabilitation and as individual needed. At the admission, patient was assessed by a rehabilitation team who defined a specific program according to the framework of the international classification of functions of WHO (Lexell 2014; Silva 2015); and at discharge, a clinical evaluation was made to determine the functional improvement of patients.

Statistical analysis

We completed statistical comparisons for each of the demographic and clinical parameters mentioned above. The analysis is based on the Kruskal Wallis rank test for continuous variables and on the Chi Square value for categorical variables. Correlations among variables were tested with the Spearman correlation coefficient (rho) and linear regression models were used to test the impact of cognitive status ad admission on functional recovery. A significance level of $p < 0.05$ was set.

RESULTS

We included 80 participants with TBI: 19 (23.75%) were females (34.55±14.59 years old) and 61 (76.25%) were male (35.82±15.23 years old).The three classes (LCF 2-3, LCF 4-6, LCF 7-8) at admission were comparable for sex, physical limitations (limb fractures, spasticity, paraosteoarthropathy) and motor impairment (right hemiplegia, left hemiplegia, tetraplegia and motor disorders . Conversely, we observed differences across the groups with respect to age (p = 0.024), GCS score (p = 0.005), phase of rehabilitation (p = 0.001) and clinical outcome (FAC, LCF, GOSE, tFIM score, mFIM, cFIM) (p = 0.001). Specifically, the more cognitive impaired group (LCF 2-3) was younger, with a lower GCS score after the TBI, was mostly admitted for rehabilitation in the subacute phase and presented poorer clinical score at admission. Differences among groups were highlighted even considering the time when RAGT was delivered respect to the admission to the rehabilitation (p=0.001). The LCF 2-3 group received RAGT later compared to the other groups during their rehabilitation stay. (See Table 1).

Table 1: Clinical and demographical characteristics

	LCF 2-3 (n=24)	LCF 4-6 (n=42)	LCF 7-8 (n=14)	total (n=80)	p
Age	29.83 (14.77)	37.87 (15.09)	37.21 (12.43)	35.32 (14.84)	0.024
Sex (F/M)	8/16	6/36	5/9	19/61	0.192
GCS score	4.33 (1.73)	5.78 (2.03)	6.78 (2.63)	5.52 (2.22)	0.004
Rehabilitation phase:					0.001
subacute	18	18	1	37	
chronic	6	24	13	43	
Physical limitations:					0.21
limb fractures	8	15	4	27	
spasticity	14	20	6	40	
POA	1	7	2	10	
Motor impairment:					0.546
right hemiplegia	5	7	1	13	
left hemiplegia	4	9	3	16	
tetraplegia	13	22	6	41	
movement disorders	2	4	4	10	
LCF	2.5 (0.51)	5.19 (0.74)	7 (0.00)	4.7 (1.7)	0.001
GOSE	2.37 (0.49)	3.45 (0.8)	4.21 (0.58)	3.26 (0.94)	0.001
FAC	0.17 (0.64)	0.67 (1.12)	2.78 (1.25)	0.88 (1.36)	0.001
tFIM	18.58 (2.04)	41.95 (23.3)	63.71 (17.47)	28.38 (22.74)	0.001
mFIM	13.12 (0.45)	25.33 (18.09)	63.71 (17.47)	28.38 (22.74)	0.001
cFIM	6.04 (3.02)	16.52 (7.66)	31.86 (3.93)	16.06 (10.1)	0.001
Rehab-RAGT (days)	100 (78)	52 (50)	23 (27)	61 (63)	0.001
RAGT (sessions)	17.66 (11.6)	17.13 (9.45)	12.92 (5.61)	16.65 (9.78)	0.397
LOS (days)	184.55 (92.49)	157.44 (99.71)	73.30 (38.30)	153.18 (96.84)	0.001

GCS=Glasgow Coma Scale; POA=paraosteoarthropathy; LCF=Level of Cognitive Functioning; GOSE=Glasgow Outcome Scale Extended; FAC=Functional Ambulatory classification; FIM=Functioning Independence Measure: tFIM (total score), mFIM (motor domain), cFIM (cognitive domain). RAGT=Robot-Assist Gait Training, LOS= Length of Stay

The analysis showed that participants with a lower cognitive level at admission were mostly in the subacute phase of rehabilitation (p = 0.001) and had the better functional recovery. Specifically, we found an improvement not only with regards to cognition (p = 0.001), but also in walking function (p = 0.037), independence of daily living (p = 0.001), and disability (p = 0.034). These findings were not statistically different in subacute and chronic subgroups, except in relation to cognition (with p = 0.0001). See Table 2.

Table 2: Functional improvements according with cognition level at admission and rehabilitation phase.

		LCF 2-3 (n=24)	LCF 4-6 (n=42)	LCF 7-8 (n=14)	total (n=80)	p
ΔLCF	subacute	3.56 (1.25)	1.29 (0.77)	0 (0.1)	2.35 (1.52)	0.001
	chronic	2 (1.1)	0.58 (0.72)	0 (0)	0.60 (0.9)	0.0018
	total	3.16 (1.37)	0.88 (0.80)	0.00 (0.00)	1.41 (1.52)	0.001
ΔGOSE	subacute	2.56 (1.5)	1.6 (0.98)	1 (0.1)	2.1 (1.3)	0.12
	chronic	1.67 (1.51)	0.42 (0.78)	0.23 (0.44)	0.53 (0.93)	0.0495
	total	2.33 (1.17)	0.92 (0.77)	0.34 (0.47)	1.24 (1.36)	0.034
ΔFAC	subacute	2.44 (1.5)	1.89 (1.53)	2 (0.1)	2.16 (1.5)	0.47
	chronic	1 (0.6)	0.71 (0.62)	0.92 (0.64)	0.81 (0.63)	0.532
	total	2.08 (1.47)	1.21 (1.24)	1 (0.68)	1.43 (1.30)	0.037
ΔtFIM	subacute	57.06 (29.46)	45.11 (25.14)	23 (0.1)	50.32 (27.67)	0.22
	chronic	26.83 (22.78)	9.25 (9.63)	7.31 (8.01)	11.12 (13.14)	0.168
	total	49.5 (30.54)	24.62 (25.23)	8.43 (8.76)	29.25 (28.76)	0.001
ΔmFIM	subacute	39 (24.15)	33.83 (21.24)	21 (0.1)	36 (22.39)	0.62
	chronic	18.33 (18.4)	6.17 (6.56)	7 (7.44)	8.12 (9.86)	0.24
	total	33.83 (24.25)	18.02 (20.27)	8.96 (8.06)	21.01 (21.81)	0.001
ΔcFIM	subacute	17.94 (7.53)	11.22 (6.86)	2 (0.1)	14.24 (8.04)	0.012
	chronic	8.5 (6.28)	3.08 (4.54)	0.31 (0.63)	3 (4.76)	0.0163
	total	15.58 (8,24)	6.57 (6.90)	0.43 (0.75)	8.2 (8.56)	0.001

LCF=Level of Cognitive Functioning; GOSE=Glasgow Outcome Scale Extended; FAC=Functional Ambulatory classification; FIM=Functioning Independence Measure: tFIM (total score), mFIM (motor domain), cFIM (cognitive domain).Δ=Symbol of variation

Evidence of greater gains was demonstrated in patients in the subacute rather than chronic rehabilitation phase in all clinical outcomes: LCF (p =0.001); GOSE (p=0.003); FAC (p=0.038) and FIM (p=0.001). (See Fig 10)

Figure 10: Clinical variation in function of Rehabilitation Phase

The level of cognitive function at admission was strongly correlated with the increase in the level of cognitive function at discharge (rho = - 0.83; p = 0.001), moderately with ΔGOSE (rho = - 0.57; p = 0.001), ΔtFIM (rho = - 0.56; p = 0.001), ΔcFIM (rho = - 0.65; p = 0.001) fair with ΔmFIM (rho = - 0.46; p = 0.001) and ΔFAC (rho = - 0.33; p = 0.003). We concluded that the level of cognition at admission can explain the 68.15% of the cognitive improvement (R^2 = 0.68; β = - 0.74, p = 0.001); 32.74% of the disability improvement (R^2 = 0.33; β = - 0.34, p = 0.001); 30% of functional ability improvement (R^2 = 0.3; β = - 9.31, p = 0.001) including 22% motor and 42% cognitive ability, and also responsible for 11% of the improvement in gait (R^2 = 0.11; β = - 0.25, p = 0.003). See Table 3.

Patients with disorders of consciousness have had longer period to recover and longer period to receive the RAGT. More the level of cognition was lower, longer was the period of recover and the period to receive the RAGT (p=0.001). The total number of RAGT sessions did not have influence on the level of consciousness of different patients (p=0.397) (Table 1); and a weak correlation has been observed between RAGT sessions and FIM recovery (rho= 0.2).

Table 3: Impact of the cognitive level at admission on functional recovery.

	DF	rho	R-Square	B	t	P
ΔGOSE	79	- 0.568	0.3274	-0.337	- 6.16	0.000
ΔFAC	79	-0.329	0.1081	-0.251	- 3.07	0.003
ΔLCF	79	-0.8259	0.6815	- 0.74	- 12.92	0.000
ΔtFIM	79	-0.5558	0.3033	-9.31	- 5.83	0.000
ΔmFIM	79	- 0.4584	0.2159	-5.956	- 4.63	0.000
ΔcFIM	79	- 0.652	0.4259	-3.283	-7.61	0.000

R-Square = coefficient of determination; DF = degree of freedom; B= slope of regression= probability; rho= coefficient of correlation; rho: coefficient of correlation.

DISCUSSION

The sequelae resulting from a severe TBI are not only those related to function but also to cognitive, mental and emotional aspects. For this reason, all these elements must be considered by the rehabilitation processes (Barman et al. 2016; Lapitskaya et al. 2011; Leary 2018). The aim of this work was to produce a comprehensive analysis using demographic and clinical parameters to investigate the impact of the LCF at admission on RAGT and the functional recovery in terms of walking independence, cognitive level, independence of daily living and disability. With the RAGT introduction in rehabilitation as option for delivering a high-intensity for persons affected for severe Brain injury (Esquenazi 2012; Straudi 2020; Esquenazi 2013), nothing is not clear concerning the level of consciousness of patients with TBI and the RAGT practice.

Following the outcomes observed, patients with disorders of consciousness at admission has a greater improvement at discharge, particularly in cognitive function ($p = 0.001$). However, we noticed that they were relatively younger (under 30 years old) and age is an important factor in functional recovery during TBI rehabilitation (Flanagan 2005; Rothweiler 1998; Testa 2005). Several studies have shown the ability of young patients to integrate new knowledge and learning skills (Fraser 2019; Testa 2005). Patients of this age class seemed more exposed; they were severely injured during the TBI event. The GCS which is an indicator of the severity of the event and which reflects the violence of the event TBI was more accentuated versus other age groups ($p = 0.004$) (Teasdale et al. 1974). This aspect justify the large period of these patients in the hospital (LOS) ($p=0.001$) and the large timing between the event to RAGT training ($p=0.001$) (Elwood et al. 2009). This crucial period is necessary to overcome biological and psychological insufficiencies that could negatively condition any progress in the recovery process. Moment especially dedicated to multidisciplinary rehabilitation and in which is highlighted the impact targeted for each patient.

In addition, we observed an important difference in relation to the phase of rehabilitation, as previously highlighted, patients who receive RAGT during a multidisciplinary rehabilitation in the subacute phase of recovery had a more favourable outcome in terms of functional recovery (Straudi et al. 2020). In our TBI sample, among patients with disorders of consciousness there were more in their first 6 months since injury (75%) than others (41.85 and 7.13%). The consciousness disorder seems not to be an obstacle to the RAGT; but an asset to cognitive relearning especially in young patients in the subacute phase after of course a period of patient stabilization. The high percentage of patients in subacute with disorders of consciousness would have influenced the improvement of clinical parameters especially in this highly impaired population and moderately in the other groups, except for the level of cognition.

However, a slow recovery of consciousness can be detected even in a longer period (Andelic et al. 2012); these outcomes explain the role of RAGT in the recovery of patients in the subacute phase with varying cognitive levels at admission. Conversely, we did not find differences among groups in chronic TBI. This is explained by the fact that during the rehabilitation, chronic patients experience difficulties in relearning new behavior; because habits that have already developed are difficult to be replaced (Leary et al. 2018).

To date, few studies indicate the feasibility of RAGT during rehabilitation of severe TBI with disorders of consciousness (Lapiskaya 2011; Williams 2019) further investigations are necessary.

Establishing its positive impact on the functional improvement of patients with severe TBI would be one of the indicators of its usefulness. Cognitive impairments are present in a high proportion of patients following a TBI (Benedictus 2010; Rabinowitz 2014); conventional treatment combined with RAGT would be a possible solution for improving functional, mental, physical and emotional impairments (Leary 2018; Zarshenas 2019).

In our cohort, the cognitive level at admission influenced the rehabilitation length of stay (LOS) and the time needed to receive RAGT during the multidisciplinary rehabilitation programme.As previously reported, patients with disorders of consciousness need longer period to recover and similarly, a longer period to be able to safely receive the RAGT was necessary (Zarshenas 2019; Novak 2001; Kavusipur 2013; Katz 2009). Regarding the RAGT intensity parameters, no significant effects on the dose were reported ($p=0.397$), reflecting how the level of cognitive impairment does not modify the number of RAGT sessions received; contrary to what we would have liked on the basis of previous studies in terms of motor functional recovery concerning other types of brain injury (Straudi et al 2020; Lapitskaya et al. 2011).

This observational study is limited by the fact of his retrospective aspect firstly, and the fact that we cannot clearly establish a direct cause-effect relationship between RAGT and the cognitive level on functional improvement in patients with severe TBI. Nonetheless, with this work we highlight the feasibility and positive effects of RAGT combined with a multidisciplinary rehabilitation program in these patients, especially those with a disorder of consciousness at admission. Therefore, the level of consciousness could delay the accessibility of severe TBI patients to the RAGT, but, we hypothesize that the patients' consciousness at admission would not interfere in the process of functional recovery as well as in the RAGT training protocol. This study suggests the need for further analysis by

Prospective and clinical studies to better understand impact cognitive level at admission on functional recovery and RAGT training in patients with severe TBI in multidisciplinary rehabilitation.

CONCLUSION

Robot assisted gait training offers an intensive training and a deeper understanding of its outcomes can help define its clinical applicability. There is some evidence of a change in functional patterns at discharge. We observed, over time, functional improvement principally in cognitive function, which may indicate a broader improvement, although other heterogeneous factors (age, rehabilitation phase) may have influenced recovery. The cognitive level at admission influence the rehabilitation length of stay (LOS) and the time needed to receive RAGT during the multidisciplinary rehabilitation programme. The number of RAGT sessions received is not correlated to the level of cognitive impairment. However the cognitive level at admission without heterogeneous factors seems to be an important indicator of functional recovery. These supports do not exclude the role of RAGT or the impossibility of functional recovery in the rehabilitation of subacute patients with severe TBI with loss of consciousness; contrary, these findings support the multidisciplinary process and the possibilities of functional gain in these patients.

References

Andelic N, Bautz-Holter E, Ronning P, Olafsen K, Sigurdardottir S, Schanke AK et al. Does an Early Onset and Continuous Chain of Rehabilitation Improve the Long-Term Functional Outcome of Patients with Severe Traumatic Brain Injury? J Neurotrauma. 2012; 29(1). Doi: 10.1089/neu.2011.1811.

Barman A, Chatterjee A, BhideR. Cognitive Impairment and Rehabilitation Strategies After Traumatic Brain Injury.Indian J Psychol Med. 2016; 38(3): 172–181. Doi: 10.4103/0253-7176.183086.

Benedictus MR, Spikman JM, Joukje van der Naalt. Cognitive and behavioral impairment in traumatic brain injury related to outcome and return to work. J Arch PM&R. 2010; 91(9):1436–41 doi.10.1016/j.apmr.2010.06.019.

Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M et al.Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review.J. Neurotrauma. 2018 doi.org/10.1089/neu.2015.4126.

Corrigan JD, KipSmith-Knapp,Granger CV. Validity of the functional independence measure for persons with traumatic brain injury. 1997; 78(8): 828-834. Doi: 10.1016/S0003-9993(97)90195-7.

Dehem S, Stoquart G, Montedoro V. The contribution of new technologies in the motor and cognitive rehabilitation of brain-injured patients. PM&R. 2017; 99-101.

Elwood D, Rashbaum I, Bonder J, Pantel A, Berliner J, Yoon S. Et al. Length of Stay in Rehabilitation is Associated With Admission Neurologic Deficit and Discharge Destination. PM&R. 2009 1(2):147-51.

Esquenazi A & Packel A. Robotic-Assisted Gait Training and Restoration. American Journal of Physical Medicine & Rehabilitation. 2012; 91(11): 217–231. Doi:10.1097/PHM.0b013e31826bce18.

Esquenazi A, Lee S, Packel AT, Braitman LA. Randomized Comparative Study of Manually Assisted Versus Robotic-Assisted Body Weight Supported Treadmill Training in Persons With a Traumatic Brain Injury. American Academy of Physical Medicine and Rehabilitation. 2013; 5(4): 280-290.Doi:10.1016/j.pmrj.2012.10.009.

Esquenazi A, Lee S, Wikoff A, Packel A. Toczylowski T, Feeley J. A Comparison of Locomotor Therapy Interventions: Partial-Body Weight-Supported Treadmill, Lokomat, and G-EO Training in People With Traumatic Brain Injury. American Academy of Physical Medicine and Rehabilitation. 2017; 9(9): 839-846. Doi:10.1016/j.pmrj.2016.12.010.

Flanagan SR, Hibbard MR, Gordon WA. The impact of age on traumatic brain injury. Phys Med Rehabil Clin N Am. 2005; 16(1):163-177.Doi:10.1016/j.pmr.2004.06.012.

Fraser EE, Dowing MG, Biemacki K, MC Kenzie DP and Ponsford JL. Cognitive Reserve and Age Predict Cognitive Recovery after Mild to Severe Traumatic Brain Injury. J Neurotrauma. 2019; 36(19): 2753-2761. Doi: 10.1089/neu.2019.6430.

Katz DI, Polyak M, Coughlan D, Nichol N. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up. Prog Brain Res. 2009; vol. 177: 73-88.Doi.org/10.1016/S0079-6123(09)17707-5 .

Kavusipur S , Shirazi ZR, Ardekani Z and Omidi S. Prediction of Consciousness Recovery in Coma after Traumatic Brain Injury by Disorder of Consciousness Scale (DOCS). Bull Emerg Trauma. 2013 1(2): 86–89.

Lapitskaya N, Nielsen JF and Frederiksen AF. Robotic gait training in patients with impaired consciousness due to severe traumatic brain injury. J Brain Injury. 2011; 25(11): 1070-79. Doi:10.3109/02699052.2011.607782.

Leary JB, Kim GY, Bradley CL, Hussain UZ, Sacco M, Bernad M et al. The Association of Cognitive Reserve in Chronic-Phase Functional and Neuropsychological Outcomes Following Traumatic Brain Injury. Journal of Head Trauma Rehabilitation.2018; 33(1): E28–E35. Doi: 10.1097/HTR.0000000000000329.

Lexell J, Brogardh C. The use of ICF in the neurorehabilitation process.. Neurorehabilitation. 2014 ; 36(1). DOI: 10.3233/NRE-141184.

McLafferty FS, Barmparas G, Ortega A, Roberts P, Ko A, Harada M, Black kL and Ley EJ. Predictors of improved functional outcome following inpatient rehabilitation for patients with traumatic brain injury. NeuroRehabilitation. 2016 ; 39(3): 423-30. Doi: 10.3233/NRE-161373.

Nolan KJ, Karunakaran KK, Ehrenberg N, Kesten AG. Robotic Exoskeleton Gait Training for Inpatient Rehabilitation in a Young Adult with Traumatic Brain Injury. Conf Proc IEEE Eng Med Biol Soc. 2018; 2018:2809-2812. Doi:10.1109/EMBC.2018.8512745.

Novak TA, Bush BA, Meytaler JM and Canupp K. Outcome after traumatic brain injury: Pathway analysis of contributions from premorbid, injury severity, and recovery variables. Arch Phys Med Rehabil. 2001; 82(3): Pages 300-305. Doi: 10.1053/apmr.2001.18222.

O'Brien A, Dester CA, Scarton A , O'Brien JM. Robotic-assisted Gait Training as Part of the Rehabilitation Program in Persons with Traumatic and Anoxic Brain Injury. PMR.2016; 97(10): e117. Doi:10.1016/j.apmr.2016.08.366

Rabinowitz AR, Levin H S.Cognitive Sequelae of Traumatic Brain Injury. Psychiatr Clin North Am. 2014; 37(1): 1–11 doi: 10.1016/j.psc.2013.11.004.

Riener R, Lùnenburger L, Maier IC, Colombo G, Dietz V. Locomotor training in subjects with sensory-motor deficit: an overview of robotic gait orthosis Lokomat. Health care engineering. 2010; 1(2): 197-216. Doi: 10.1260/2040-2295.1.2.197.

Rothweiler B, Temkin NR and Dikmen SS. Aging effect on psychosocial outcome in traumatic brain injury. Arch PM&R. 1998; 79(8) 881-887. Doi: 10.1016/S0003-9993(98)90082-X.

Silva SM, Correa FI, De Morais Faria CDC, Buchalla CM, Da Costa Silva PF, Corea JCF. Evaluation of post-stroke functionality based on the International Classification of Functioning, Disability, and Health: a proposal for use of assessment tools.. J Phys Ther Sci. 2015; 27(6): 1665–1670. Doi: 10.1589/jpts.27.1665.

Smania N, Avesani R, Roncari L, Ianes P, Girardi P, Varalta V et al. Factors Predicting Functional and Cognitive Recovery Following Severe Traumatic, Anoxic, and Cerebrovascular Brain Damage. JHTR. 2013; 28(2): 131–140. Doi: 10.1097/HTR.0b013e31823c0127.

Smith-Knapp K, Corrigan JD, Arnett JA. Predicting functional independence from neuropsychological tests following traumatic brain injury. JournalBrain Injury. 1996 10(9); 651-662. Doi:10.1080/026990596124070.

Straudi S, Severini G, Da Roit M, Pizzongolo LDM, Martinuzzi C and Basaglia N. The dose of robot-assisted gait therapy may influence functional recovery in a multidisciplinary rehabilitation program: an exploratory retrospective study. Int J Rehabil Res. 2020;43(2):175-182. Doi:10.1097/MRR.0000000000000407.

Stuss DT.Traumatic brain injury: relation to executive dysfunction and the frontal lobes. Jcurrent Opinion in Neurology. 2011; 24(6):584-589.Doi:10.1097/WCO.0b013e32834c7eb9.

Teasdale G, Jennett B.Assesment of coma and impaired consciousness: a practical scale. Lancet journal health. 1974; 304(7872): 81-84. Doi:10.1016/S0140-6736(74)91639-0.

Testa JA, Malec JF, Moessner AM, Brown AW. Outcome After Traumatic Brain Injury: Effects of Aging on Recovery. PM&R. 2005; 86(9): 1815–1823. Doi: 10.1016/j.apmr.2005.03.010.

Van Hedel HJA, Severini G, Scarton A, O'Brien A, Reed T, Gaeblert D et al. Advanced Robotic Therapy Integrated Centres (ARTIC): an International collaboration facilitating the application of rehabilitation technologies. Journal neuroengineering and rehabilitation. 2018; 15(1): 30. Doi: 10.1186/s12984-018-0366-y.

Williams K, Christenbury J, Niemeier JP, Newman M and Pinto S. Is Robotic Gait Training Feasible in Adults With Disorders of Consciousness? JHTR. 2019. Doi: 10.1097/HTR.0000000000000523 PMID: 31479078.

Zarshenas S, Colantonio A, Horn SD, Jaglal S, Cullen N, Cognitive and Motor Recovery and Predictors of Long-Term Outcome in Patients With Traumatic Brain Injury. Arch Phys Med Rehabil. 2019; 100(7): 1274-1282. Doi: 10.1016/j.apmr.2018.11.023

2.2 **Beneficial effects of robot-assisted gait training on functional recovery in women after stroke: a cohort study.** Lamberti N, Manfredini F, Lissom LO, Lavezzi S, Basaglia N, Straudi S. *Manuscript ID: medicina-1405907 - Accepted for Publication. Journal MDPI. https://www.mdpi.com/journal/medicina/special_issues/Acute_Ischemic_Stroke*

Abstract

Objective: This study aims to determine the gender-related response to robot-assisted gait training in a cohort of subacute stroke patients.

Design: Two-hundred thirty six participants (145 males) admitted to a rehabilitation facility after stroke, performed a robot-assisted gait training (RAGT) within a multidisciplinary rehabilitation program. Functional independence measure (FIM) and Functional Ambulatory Category (FAC) were assessed at admission and discharge to determine gender-related outcomes.

Results: At baseline no significant difference among genders in terms of clinical and demographic parameters (FAC, FIM, type of stroke and age) were observed. At the end of rehabilitation both males and females exhibited significant improvements for both FIM (71% males and 80% females reaching the MCID cutoff value; $p = 0.15$) and FAC (Δscore: males 1.9±1.0; females 2.1±1.1; $p=0.11$) where a greater, still not significant improvement was observed for women. Among the factors related to a clinically significant improvement, gender was never retained in regression models.

Conclusion: Among subacute stroke patients equal adherence and benefits were observed following RAGT training in both gender. These data support the use of gait robotics for female patients to favor participation and functional recovery.

Key words: gender, Stroke, multi-disciplinary rehabilitation, robot-assisted gait training

What is known?

After stroke, women experienced higher level of disability with a perceived poorer quality of life compared with males. Similarly, gender differences among rehabilitative interventions should be explored in order to propose highly personalized treatments.

What is New?

Despite of women tended to experience more frequently physical impairments and limitation in activities after stroke, no gender differences were highlighted in subacute stroke patients who underwent robot-assisted gait training during a multidisciplinary rehabilitation program in terms of walking and functional independence.

Introduction

Stroke, a leading cause of death and long-term disability (Mehrholz et al. 2020) poses a great burden on women. After stroke, women showed better survival but more disability and poorer quality of life compared with males (Carcel et al. 2019). Similarly, in the presence of conflicting data on functional recovery (Gargano JW et al. 2007; Gall SL et al.2012), more frequent presence of physical impairments and limitations in activities of daily living (Gal SL et al.2012), depression (Erikson et al. 2004), fatigue (Glader et al. 2002) and worse cognitive outcomes were reported in women (Gargano JW et al 2007; Gall SL et al. 2012).

In stroke survivors the mobility is often limited by the walking impairment (Taveggia et al. 2016; Eng JJ et al. 2007) and restoration of walking ability and gait rehabilitation are highly relevant objectives of the rehabilitation process (Bohannon et al. 1991).

In recent years, the introduction of robotics (Warraich et al. 2010; Mehrholz et al. 2017) showed interesting rehabilitative outcomes for stroke survivors (Kwakkel et al. 1991; Van Peppen et al.2004) offering an alternative to the conventional rehabilitation (Lafont et al 2014). Robotic rehabilitation provides intensive, task-oriented, repeated (Veerbeek et al. 2014; Duncan et al 2011) and personalized work for favoring recovery and plasticity-dependent response of stroke survivors (Cho JE et al. 2018; Wolpert et al. 2011). In addition, the robotic system, allowing partial or total body weight bearing, enables the enrolment of non ambulatory patients (Iosa et al. 2011) and the prevention of falls during the training sessions (Cho JE et al. 2018). In chronic stroke patients (as for other neurologic diseases (Straudi et al. 2020), studies failed to demonstrate a more favorable impact of electromechanically- or technology-assisted gait training on recovery compared to conventional over ground gait training (Wall et al. 2019; Hsu Cy et al 2019) or its effectiveness in combination with physiotherapy to achieve independent walking (Mehrholz et al. 2017; Moncheboeuf G et al. 2020). However, an effectiveness of robotic training was reported on non ambulatory rather than for ambulatory stroke patients (Mehrholz et al. 2017; Cho JE et al 218), suggesting that this approach might represent a rehabilitative strategy for targeted populations.

Rehabilitation is a critical issue for women. A lower response or adherence to rehabilitation for various chronic diseases (Arthur et al. 2013; Foy CG et al. 2001) has been reported, possibly due to interest, comorbidities, or rehabilitation strategies (Dorenkamp et al. 2016; Gommons et al. 2019; Manfredini R et al. 2019; Hyun et al. 2020). After stroke, sexwas associated to lower post-stroke physical activity (Thilarajah et al. 2017) and different improvements in physical function following home-based rehabilitation among home-dwelling patients (Chi NF et al. 2020). Interestingly, in a randomized trial comparing RAGT versus conventional training in a population of neurologic patients including also stroke patients, walking recovery in RAGT group was significantly improved among females compared with males (Morone et al. 2014). Being a woman was also a significant predictor of clinically significant changes in robot assisted stroke rehabilitation for upper arm [Hsieh et al. 2014).

Considering the known sex differences in occurrence and severity of stroke, as for therapies (Sohrabji et al. 2017), also rehabilitation should consider possible sex differences in treatment.

The retrospective study aims to present the results attained in terms of functional recovery in a cohort of subacute stroke patients who received RAGT during a multidisciplinary rehabilitation program. The study specifically aims to report the response of females to understand the impact of RAGT as possible targeted strategy in stroke rehabilitation.

Methods.

We retrospectively analyzed a prospectively collected dataset of patients with subacute stroke and admitted to an inpatient multidisciplinary rehabilitation at the Department of Physical and Rehabilitation Medicine at University Hospital of Ferrara, Italy. Ethics committee CE-AVEC approved the study, but written informed consent was not collectable from all patients since part of them was no longer attending the rehabilitation clinics.

Subjects

Subacute stroke patients that underwent a multidisciplinary rehabilitation program between May 2007 and April 2018 were studied.

Inclusion criteria were: male and female patients aged > 18 years; ischemic or hemorrhagic stroke onset within 180 days from rehabilitation admission; Functional Ambulatory Category (FAC) and Functional independence measure (FIM) at the entry ≤3 and ≤90 respectively.

Exclusion criteria were: impossibility to perform RAGT due to medical instability, severe cognitive impairments, and severe lower limb spasticity or skin lesions.

Interventions

All patients during the hospital stay underwent RAGT using Lokomat treadmill (Hocoma AG, Volketswil, Switzerland). During these sessions subjects wore a harness attached to a system to provide body weight support and they walked on the treadmill with the help of a roboticdriven gait orthosis. The legs are guided according to a physiological gait pattern with the possibility to adjust the torque of the knee and hip drives. Each training sessions lasted for an hour with 30-min of real walking time due to the setup time. During the first treatment session, the parameters are set according to the patient's functional characteristics, however, for the patients included in the study, a 50% relief of body weight and 100% of assistance provided by the robot were scheduled (Artic 2018). Treadmill speed, body weight support and guidance force were progressively adjusted during training progression. Training lasted for a minimum of 7 sessions, with variable frequencies (1-5 times/week).

Concomitantly, all patients benefited from a multidisciplinary rehabilitation program defined according to patient individual's needs (conventional motor rehabilitation, occupational therapy, speech and cognitive therapy).

Outcomes

A dataset containing information about patients' demographic, stroke characteristics, days from stroke to rehabilitation, length of hospital stay, number of RAGT session was compiled.

The outcomes of the study were the FIM, considering both its total score (FIMtot) and the motor (FIMmot) and cognitive (FIMcogn) domains, and the FAC. The FIM is an 18-item, clinician-reported scale that assesses function in six areas including self-care, continence, mobility, transfers, communication, and cognition. Each item is rated on a 7-level classification by an experience therapist (Linacre et al. 1994). To the purposes of this study, the minimal clinically important difference (MCID) for FIM total score was 22 according to Beninato et al (Beninato et al. 2006).

The FAC is a functional walking test that evaluates ambulation ability through a 6-point scale by determining how much human support the patient requires when walking (Mehrholz et al 2007). Both scales were collected at admission to the rehabilitation facility, and at discharge.

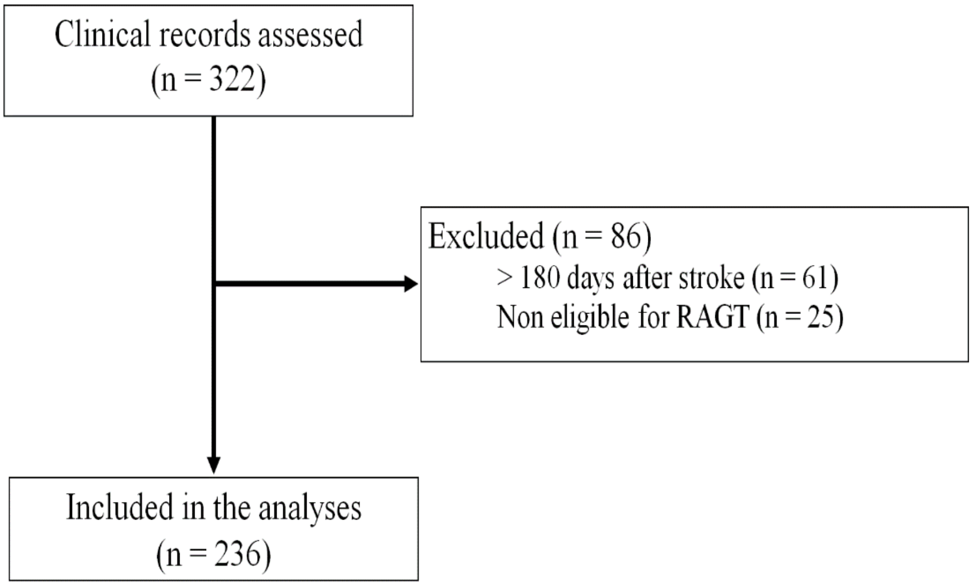
Statistical analysis

The data distribution was verified through the Shapiro-Wilk test. The baseline comparison between the two groups (male and females) was obtained through a chi-squared test for categorical variables, or an independent samples t-test or Mann-Whitney test for continuous variables. Within-group comparison was performed via paired samples t-tests or Wilcoxon tests and between-group comparisons for all outcomes were obtained again with independent samples t-tests or Mann-Whitney tests according to data distribution. A p value < 0.05 was considered statistically significant. Data analyses were performed with MedCalc statistical software version 19.2 (MedCalc Software Ltd, Ostend, Belgium).

Results

322 stroke patients admitted in the rehabilitation clinics from 2007 to 2018 who received RAGT were assessed for eligibility. Eighty-six patients were excluded because they did not matched the inclusion criteria (Figure 11).

Figure 11: Flow Diagram of participants



Within the analysed sample of patients, 91 were females (39%) and 145 males (61%).

Clinical and demographic characteristics at admission of rehabilitation

At the admission, the two groups were not different in terms of demographics nor clinical characteristics. Also the outcomes measures FIM and FAC were balanced between the two groups. (Data are reported in Table 4).

Table 4: Characteristics of the two groups of patients at the hospital admission

	Males (n = 145)	**Females (n = 91)**	**p**
Age, years	63±10	62± 14	0.74
Ischemic stroke, n (%)	90 (62)	56 (60)	0.68
Hemorrhagic stroke, n (%)	55 (38)	35 (40)	0.72
Days since stroke	80±41	82±48	0.69
FIM, total score	47±19	45±19	0.54
FIM, motor component	24±12	25±11	0.94
FIM, cognitive component	22±10	21±9	0.46
FAC	0.4±0.6	0.3±0.7	0.16

Abbreviations: FIM: functional independence measurement; FAC: functional ambulatory classification.

Differences in rehabilitation treatment

Both groups showed a comparable length of hospital stay, calculated at 108±60 days for males and 102±56 days for females (p=0.41). In addition, a similar number of RAGT sessions were executed between groups, with a mean of 15±8 for males compared to 14±8 for females (p=0.22).

Finally, both groups showed the same RAGT frequency per week of 2±1 sessions (p = 0.65) suggesting that a comparable amount of RAGT rehabilitation was given to both groups of patients.

Comparison of outcomes

Both groups significantly improved all the mobility scales considered in the study (Table 5). No between-group differences were observed for all outcomes, except for females that exhibited a higher FAC variation, approaching statistical significance (p = 0.11) (Figure 12).

In addition, the MCID for FIM scale, exhibited no gender differences, with 71% of man and 80% of women reaching the cutoff value (p = 0.15).

Finally, at the end of rehabilitation, 28 (19%) males and 17 females (19%) reached the gait independence (defined as FAC ≥4), again without any between-group difference (p=0.90).

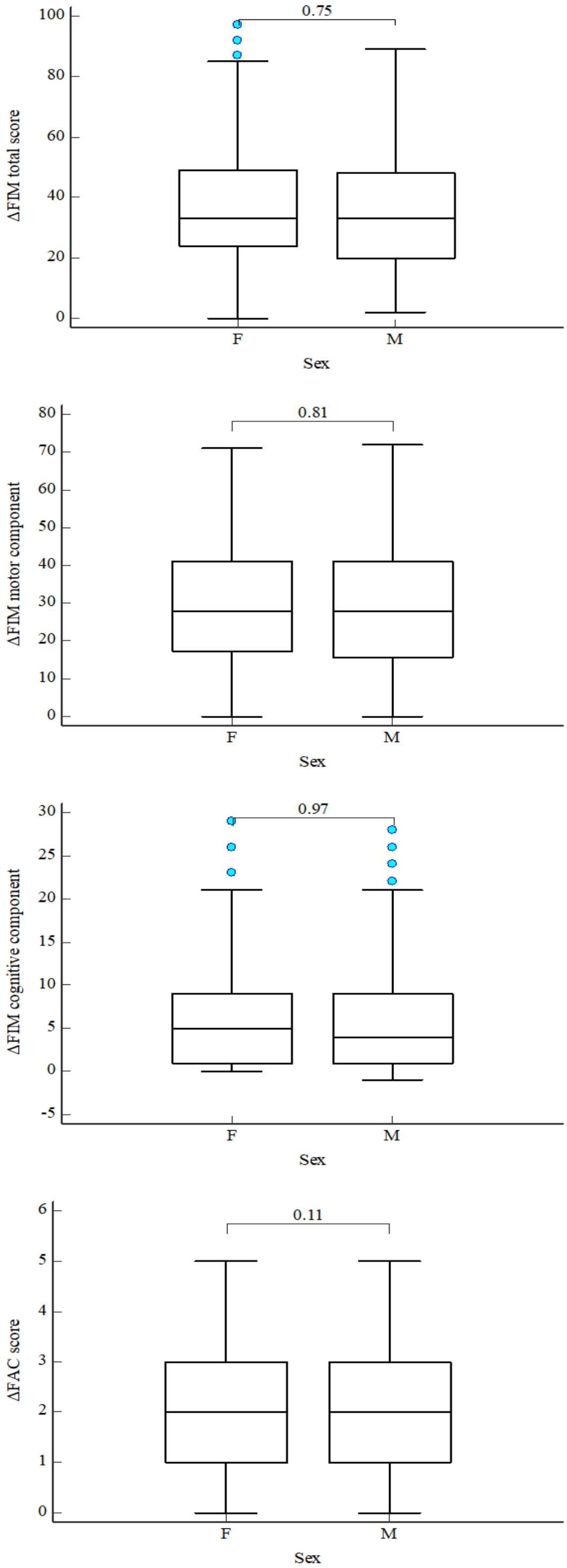
Table 5:Clinical Outcomes of the study for the two groups

	Males (n = 145)		**Females (n = 91)**		**Between-group p**
	Admission	*Discharge*	*Admission*	*Discharge*	
FIM, total	47±19	82±24**	45±19	81±26**	0.75
FIM, motor	24±12	54±20**	25±11	54±20**	0.81
FIM, cognitive	22±10	29±7**	21±9	28±7**	0.97
FAC	0.4±0.6	2.3±1.4**	0.3±0.7	2.4±1.3**	0.11

Abbreviations: FIM: functional independence measurement; FAC: functional ambulatory classification.

Legend: paired-samples t-tests or Wilcoxon tests, as appropriate: *p < 0.05; **p < 0.01

Figure 12: Box-plots for FIM and FAC variations in the two groups



Factors related to functional improvement after RAGT

Logistic regression models carried out in the entire population never retained gender as a significant variable. In particular, for the MCID variations in FIMtot score, a weak significant model was observed ($R^2 = 0.13$; $p < 0.001$) with only age (odds ratio: 0.95; 95% CI 0.92 to 0.98) and days from stroke to rehabilitation (odds ratio: 0.98; 95% CI 0.98 to 0.99) as the only variables retained.

A similar model was observed for FAC values ≥ 4 at the end of rehabilitation ($R^2 = 0.28$; $p < 0.001$) again with age (odds ratio: 0.91; 95% CI 0.87 to 0.94) and days from stroke to rehabilitation (odds ratio: 0.98; 95% CI 0.97 to 0.99) as the only variables included.

Discussion

This 10-year single-center retrospective study carried out in a large population of subacute stroke survivors admitted to a rehabilitation facility highlighted a good adherence to robot-assisted gait training and a favorable response in terms of gait parameters without any gender difference.

The study offers several points of discussion to be addressed.

Scientific literature report conflictive findings in relation to functional and quality of life recovery after stroke in women. In particular, several papers reported a worst outcome for women after rehabilitation (Garganoet al. 2007; Persky et al. 2010; White BM e al. 2018), while other observed similar or better improvements for females compared to males (Khattab et al. 2020; Scrutinio et al. 2020). Our study confirmed the most recent observations with superimposable results between the two sexes for all FIM scores, and also for FAC scores, where a slightly better results, despite not significant ($p = 0.11$), was noted for women. In this regards, it is noteworthy that in our study the total variation in FAC score was almost 4-fold greater than the mean variation of 0.51 reported in a recent meta-analysis (Moncheboeuf et al. 2020), again without any gender difference. Several aspects may have influenced this finding, as a lower FAC level at baseline in our population, or the different number of RAGT sessions completed in the different trials, or simply the fact that in our study the FAC variation was determined at the admission and at discharge from a rehabilitation unit, instead of immediately before and after RAGT treatment.

Concerning robot-assisted gait training, in the 2016 AHA guidelines (Wintein CJ et al. 2016) RAGT achieved an IIb class of recommendation with an A level of evidence to improve motor function and mobility after stroke in combination with conventional therapy. In our study, in absence of objective measures of physical functioning, RAGT proved to be effective with a 75% of subacute stroke that reached the minimal clinically important difference for FIM total score, and with 19% of patients that reached an autonomous ambulation, defined by a FAC score ≥ 4, confirming previous results reported in several literature reviews [Cho JE et al. 2018; Moncheboeuf et al 2020; Tedla et al. 2019). Also for the number of subjects that reached the MCID, no gender differences were reported and gender was never retained as significant factors in multiple regression models. Anyway, rehabilitation remains an important issue to be studied in women, because if on the one hand physical exercise and rehabilitation are extremely effective for functional recovery, on the other hand, women showed significantly lower adherence to the rehabilitation proposed in several disease, including stroke (Arthur et al. 2019; Gommons et al. 2015; Hyun etal. 2020). In particular, in chronic obstructive pulmonary disease and cardiovascular diseases including peripheral artery disease, women are less likely to engage in, or sustain, regular physical activity (Dorenkamp et al.2016; Gommons et al. 2015). In some of these study women showed also worst outcomes, whereas in others, especially when the exercise was carried out home-based, similar improvements were observed compared to males (Manfredini R et al. 2019). This aspect opens another important field of discussion, as the rehabilitation in chronic stroke survivors that have to ensure the maintenance of the mobility and functional independence after the in-hospital phase. Both home-based and community-based intervention has proved their effectiveness, (Thilarajah et al 2017; Lamberti N et al. 2017; Malagoni et al. 2018; Saunders et al. 2020) but in this context, the gender differences need to be further investigated.

The study presents several limitations. At first, it is a retrospective study that encompassed a concomitant rehabilitation treatment in addition to RAGT during the hospital stay; in addition, the outcome measures were collected only at the entry and at discharge, and objective measures of physical functioning were not reported.

In conclusion, a conventional rehabilitation treatment empowered by RAGT ensured in subacute stroke patients good results in terms of gait recovery, without any gender differences for all parameters considered. Further prospective study is needed to confirm the presented results.

REFERENCES

Arthur HM, Blanchard C, Gunn E, Kodis J, Walker S, Toner B. Exercise trajectories of women from entry to a 6-month cardiac rehabilitation program to one year after discharge. Biomed Res Int. 2013; 2013: 121030. Doi: 10.1155/2013/121030.

Beninato M, Gill-Body KM, Salles S, Stark PC, Black-Schaffer RM, Stein J. Determination of the minimal clinically important difference in the FIM instrument in patients with stroke. Arch Phys Med Rehabil. 2006; 87(1): 32-9. Doi: 10.1016/j.apmr.2005.08.130. PMID: 16401435.

Bohannon RW, Horton MG, Wikholm JB. Importance of four variables of walking to patients with stroke. Int J Rehabil Res. 1991; 14(3): 246-50. doi: 10.1097/00004356-199109000-00010. PMID: 1938039.

Carcel C, Wang X, Sandset EC, Delcourt C, Arima H, Lindley R, Hackett ML, Lavados P, Robinson TG, Muñoz Venturelli P, Olavarría VV, Brunser A, Berge E, Chalmers J, Woodward M, Anderson CS. Sex differences in treatment and outcome after stroke: Pooled analysis including 19,000 participants. Neurology. 2019; 93(24):e2170-e2180. doi: 10.1212/WNL.0000000000008615.

Chi NF, Huang YC, Chiu HY, Chang HJ, Huang HC. Systematic Review and Meta-Analysis of Home-Based Rehabilitation on Improving Physical Function Among Home-Dwelling Patients With a Stroke. Arch Phys Med Rehabil. 2020; 101(2): 359-373. Doi: 10.1016/j.apmr.2019.10.181.

Cho JE, Yoo JS, Kim KE, Cho ST, Jang WS, Cho KH, Lee WH. Systematic Review of Appropriate Robotic Intervention for Gait Function in Subacute Stroke Patients. Biomed Res Int. 2018; 2018: 4085-298. Doi: 10.1155/2018/4085298.

Dörenkamp S, Mesters I, de Bie R, Teijink J, van Breukelen G. Patient Characteristics and Comorbidities Influence Walking Distances in Symptomatic Peripheral Arterial Disease: A Large One-Year Physiotherapy Cohort Study. PLoS One. 2016; 11(1): e0146828. Doi: 10.1371/journal.pone.0146828.

Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK; LEAPS Investigative Team. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011; 364(21): 2026-36. doi: 10.1056/NEJMoa1010790. PMID: 21612471; PMCID: PMC3175688.

Eng JJ, Tang PF. Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. Expert Rev Neurother. 2007; 7(10): 1417-36. doi: 10.1586/14737175.7.10.1417.

Eriksson M, Asplund K, Glader EL, Norrving B, Stegmayr B, Terént A, Asberg KH, Wester PO; Riks-Stroke Collaboration. Self-reported depression and use of antidepressants after stroke: a national survey. Stroke. 2004; 35(4): 936-41. doi: 10.1161/01.STR.0000121643.86762.9a.

Foy CG, Rejeski WJ, Berry MJ, Zaccaro D, Woodard CM. Gender moderates the effects of exercise therapy on health-related quality of life among COPD patients. Chest. 2001; 119(1): 70-6. Doi: 10.1378/chest.119.1.70.

Gall SL, Tran PL, Martin K, Blizzard L, Srikanth V. Sex differences in long-term outcomes after stroke: functional outcomes, handicap, and quality of life. Stroke. 2012; 43(7): 1982-7. doi: 10.1161/STROKEAHA.111.632547.

Gargano JW, Reeves MJ, Paul Coverdell National Acute Stroke Registry Michigan Prototype Investigators. Sex differences in stroke recovery and stroke-specific quality of life: results from a statewide stroke registry. Stroke. 2007; 38(9): 2541-8. doi: 10.1161/STROKEAHA.107.485482. Epub 2007 Aug 2. PMID: 17673706.

Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. Stroke. 2002; 33(5): 1327-33. Doi: 10.1161/01.str.0000014248.28711.d6.

Gommans LN, Scheltinga MR, van Sambeek MR, Maas AH, Bendermacher BL, Teijink JA. Gender differences following supervised exercise therapy in patients with intermittent claudication. J Vasc Surg. 2015; 62(3): 681-8. Doi: 10.1016/j.jvs.2015.03.076. PMID: 26304482.

Hsieh YW, Lin KC, Wu CY, Lien HY, Chen JL, Chen CC, Chang WH. Predicting clinically significant changes in motor and functional outcomes after robot-assisted stroke rehabilitation. Arch Phys Med Rehabil. 2014; 95(2): 316-21. Doi: 10.1016/j.apmr.2013.09.018.

Hsu CY, Cheng YH, Lai CH, Lin YN. Clinical non-superiority of technology-assisted gait training with body weight support in patients with subacute stroke: A meta-analysis. Ann Phys Rehabil Med. 2019; S1877-0657(19): 30153-8. Doi: 10.1016/j.rehab.2019.09.009.

Hyun K, Negrone A, Redfern J, Atkins E, Chow C, Kilian J, Rajaratnam R, Brieger D. Gender Difference in Secondary Prevention of Cardiovascular Disease and Outcomes

Following the Survival of Acute Coronary Syndrome. Heart Lung Circ. 2020; S1443-9506 (20) 30408-X. Doi: 10.1016/j.hlc.2020.06.026.

Iosa M, Morone G, Bragoni M, De Angelis D, Venturiero V, Coiro P, Pratesi L, Paolucci S. Driving electromechanically assisted Gait Trainer for people with stroke. J

Khattab S, Eng JJ, Liu-Ambrose T, Richardson J, MacDermid J, Tang A. Sex differences in the effects of exercise on cognition post-stroke: Secondary analysis of a randomized controlled trial. J Rehabil Med. 2020; 52(1):jrm00002. Doi: 10.2340/16501977-2615. PMID: 31608416.

Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet. 1999; 354(9174): 191-6. doi: 10.1016/S0140-6736(98)09477-X.

Laffont I, Bakhti K, Coroian F, van Dokkum L, Mottet D, Schweighofer N, Froger J. Innovative technologies applied to sensorimotor rehabilitation after stroke. Ann Phys Rehabil Med. 2014; 57(8):543-551. Doi: 10.1016/j.rehab.2014.08.007. Epub 2014 Aug 26. PMID: 25261273.

Lamberti N, Straudi S, Malagoni AM, Argirò M, Felisatti M, Nardini E, Zambon C, Basaglia N, Manfredini F. Effects of low-intensity endurance and resistance training on mobility in chronic stroke survivors: a pilot randomized controlled study. Eur J Phys Rehabil Med. 2017; 53(2): 228-239. Doi: 10.23736/S1973-9087.16.04322-7.

Linacre JM, Heinemann AW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the Functional Independence Measure. Arch Phys Med Rehabil. 1994; 75(2):127-32. PMID: 8311667.

Malagoni AM, Cavazza S, Ferraresi G, Grassi G, Felisatti M, Lamberti N, Basaglia N, Manfredini F. Effects of a "test in-train out" walking program versus supervised standard rehabilitation in chronic stroke patients: a feasibility and pilot randomized study. Eur J Phys Rehabil Med. 2016; 52(3): 279-87.

Manfredini R, Lamberti N, Manfredini F, Straudi S, Fabbian F, Rodriguez Borrego MA, Basaglia N, Carmona Torres JM, Lopez Soto PJ. Gender Differences in Outcomes Following a Pain-Free, Home-Based Exercise Program for Claudication. J Womens Health (Larchmt). 2019; 28(9): 1313-1321. Doi: 10.1089/jwh.2018.7113.
Mehrholz J, Thomas S, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev. 2017; 8(8): CD002840. Doi: 10.1002/14651858.

Mehrholz J, Wagner K, Rutte K, Meissner D, Pohl M. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. Arch Phys Med Rehabil. 2007; 88(10): 1314-9. Doi: 10.1016/j.apmr.2007.06.764. PMID: 17908575.

Morone G, Iosa M, Marinozzi M, D'Antonio E, Poli P, Masiero S, Molinari M, Paolucci S, Jensen W, Andersen OK, Akay M. Effectiveness of Robotic Assisted Walking Therapy: The Role of Age and Sex. In: Replace, Repair, Restore, Relieve – Bridging Clinical and Engineering Solutions in Neurorehabilitation. Springer International Publishing. 2014: 569-573.

Moucheboeuf G, Griffier R, Gasq D, Glize B, Bouyer L, Dehail P, Cassoudesalle H. Effects of robotic gait training after stroke: A meta-analysis. Ann Phys Rehabil Med. 2020; S1877-0657(20): 30065-8. Doi: 10.1016/j.rehab.2020.02.008. Epub ahead of print. PMID: 32229177.

Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. Curr Cardiol Rep. 2010; 12(1): 6-13. Doi: 10.1007/s11886-009-0080-2.

Rehabil Res Dev. 2011; 48(2): 135-46. Doi: 10.1682/jrrd.2010.04.0069. PMID: 21480088.

Saunders DH, Sanderson M, Hayes S, Johnson L, Kramer S, Carter DD, Jarvis H, Brazzelli M, Mead GE. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2020; 3(3): CD003316. Doi: 10.1002/14651858.CD003316.pub7. PMID: 32196635; PMCID: PMC7083515.

Sohrabji F, Park MJ, Mahnke AH. Sex differences in stroke therapies. J Neurosci Res. 2017; 95(1-2): 681-691. Doi: 10.1002/jnr.23855.

Straudi S, Manfredini F, Lamberti N, Martinuzzi C, Maietti E, Basaglia N. Robot- assisted gait training is not superior to intensive overground walking in multiple sclerosis with severe disability (the RAGTIME study): A randomized controlled trial. Mult Scler. 2020; 26(6): 716-724. Doi: 10.1177/1352458519833901.

Taveggia G, Borboni A, Mulé C, Villafañe JH, Negrini S. Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. Int J Rehabil Res. 2016; 39(1):29-35. doi: 10.1097/MRR.0000000000000137.

Tedla JS, Dixit S, Gular K, Abohashrh M. Robotic-Assisted Gait Training Effect on Function and Gait Speed in Subacute and Chronic Stroke Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Eur Neurol. 2019; 81(3-4): 103-111. Doi: 10.1159/000500747.

Thilarajah S, Mentiplay BF, Bower KJ, Tan D, Pua YH, Williams G, Koh G, Clark RA. Factors Associated With Post-Stroke Physical Activity: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2018; 99(9):1876-1889. Doi: 10.1016/j.apmr.2017.09.117.

Van Hedel HJA, Severini G, Scarton A, O'Brien A, Reed T, Gaebler-Spira D, Egan T, Meyer-Heim A, Graser J, Chua K, Zutter D, Schweinfurther R, Möller JC, Paredes LP, Esquenazi A, Berweck S, Schroeder S, Warken B, Chan A, Devers A, Petioky J, Paik NJ, Kim WS, Bonato P, Boninger M; ARTIC network. Advanced Robotic Therapy Integrated Centers (ARTIC): an international collaboration facilitating the application of rehabilitation technologies. J Neuroeng Rehabil. 2018; 15(1): 30. Doi: 10.1186/s12984-018-0366-y.

Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004 (8): 833-62. Doi: 10.1191/0269215504cr843oa. PMID: 15609840.

Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014; 9(2): e87987. Doi: 10.1371/journal.pone.0087987.

Wall A, Borg J, Palmcrantz S. Self-perceived functioning and disability after randomized conventional and electromechanically-assisted gait training in subacute stroke: A 6 months follow-up. NeuroRehabilitation. 2019; 45(4): 501-511. Doi: 10.3233/NRE-192929. PMID: 31868699.

Warraich Z, Kleim JA. Neural plasticity: the biological substrate for neurorehabilitation. PM&R. 2010; 2(12): S208-19. Doi: 10.1016/j.pmrj.2010.10.016. PMID: 21172683.

White BM, Magwood GS, Burns SP, Ellis C Jr. Sex Differences in Patient-Reported Poststroke Disability. J Womens Health (Larchmt). 2018; 27(4): 518-524. Doi: 10.1089/jwh.2017.6525.

Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016; 47(6): e98-e169. Doi: 10.1161/STR.0000000000000098.

Wolpert DM, Diedrichsen J, Flanagan JR. Principles of sensorimotor learning. Nat Rev Neurosci. 2011; 12(12): 739-51. Doi: 10.1038/nrn3112

2.3 Is Robot-assisted Gait Training Intensity a Determinant of Functional Recovery Early after Stroke? A Pragmatic Observational Study of Clinical Care. Lissom LO, Lamberti N, Manfredini F,Lavezzi S, Basaglia N, Straudi S. IJRR. *Article original Submitted.*

Abstract:

The aims

In this study, we wanted to identify clinical and demographic determinants of functional recovery early after Stroke that can lead to a favourable outcome in a cohort of patients with subacute stroke.

Methods:

Two-hundred thirty-six participants in subacute phase of stroke with gait disturbance (145 males) were observed during their rehabilitation. All of them underwent a full time recovery in the Unit of Physical and Rehabilitation Medicine and performed a robot-assisted gait rehabilitation (RAGT) program (Lokomat) during hospital stay. To determine effectiveness of intensity of RAGT, clinical impact (Functional Independence measure, Functional ambulatory category) were assessed at admission and discharge. In addition the type of stroke, lesion side, stroke location, duration of treatment and age, were factors of our examination in this multidisciplinary context of rehabilitation. By the MCID set for FIM on the basis of the difference between input and discharge FIM score and FAC admission (FAC<4) and in demission (FAC≥4). We established and stratified according to the number of sessions received, the proportion of good responders (GR) and newly independent patients.

Results:

Between the 236 patients included (140 ischemic and 96 hemorragic) 61.44% male and 38.56% female, 63±12 years. Ischemic other than haemorrhagic at baseline were older (p=0.019), they were early admitted in rehabilitation (P=0.013) they had less days of hospitalisation (p=0.001) and functionally we noticed a significant difference in tFIM (p=0.005)and cFIM (p=0.001). However no significant difference were observed at discharge between-group (p>0.05) excepted at cFIM (p=0.02).With total number of sessions ≥14, 74,58% totalFIM, 74.15% motorFIM, and 65.25% cognitiveFIM of patients reached MCID with regression model significant and GR: 83.5% totalFIM.

Conclusion:

Ischemic other than haemorrhagic at baseline are more functional, older and earlier, less days of hospitalization but both recover without differences except for cognitive FIM where haemorrhagic recover more. The recovery factors include the number of sessions, age and earliness.

Key words: Rehabilitation, Subacute phase, RAGT stroke, Intensity, Early rehab.

Introduction

Stroke represents, one of the most common cause of worldwide long-term disability (Penycott A et al 2012, Heshmatollah et al 2020, Kim J et al. 2019). A large number of stroke survivors have sensory motor and cognitive impairments responsible for multiple activity limitations and reduced quality of life. The burden of stroke continues to increase globally and more effective management strategies are needed to give life independence for survivors (Feigin VL et al 2015). Recurrently impairments caused by stroke are limb weakness, cognitive dysfunction, impairment of language and spatial perception. However, gait and mobility impairments represent one of the more documented sequeale (Heshmatollah et al 2020; Sheng L et al 2018; Eng JJ et al. 2007). In the last decades, several new therapeutic approaches such as robotics have been introduced in clinical practice to facilitate gait recovery. (Poli P et al 2013; Bradley et al 2020). The development of robot-assisted gait devices offered great potential for modern neurorehabilitation, based on the principles of exercise-related neuroplasticity (Warraich et al. 2010).So far Robot-assisted gait therapy have been tested successfully in patients with stroke (Hidler J et al. 2009; Duncan et al. 2011; Riener R et al 2016; Morone 2018) and is recommended in addition to a multidisciplinary rehabilitation (Melrholz 2017; Conesa L et al. 2012). Even though intensity, measured as time spent in rehabilitation activities, seems to be relevant for optimizing functional recovery (Penycott A et al 2012; Lohse 2014). Scarce evidence is available on the role of RAGT dose for functional outcomes. Recently, it has been hypothesized how dose of RAGT training may influence functional recovery in patients who undergone a multidisciplinary program (Straudi et al 2020). The aim of this pragmatic observational study was to identify the optimal dose and timing of RAGT that can lead to a favourable outcome in a sample of subacute stroke survivors. We hypothesized that patients who received a higher RAGT dose at an early stage of recovery will recover better than the others.

Materials and Methods

This is a 10 years retrospective, pragmatic cohort study that carried out at the Department of Physical and Rehabilitation Medicine at University Hospital of Ferrara, Italy. The study included patients with stroke admitted to an impatient multidisciplinary program and received a robot-assisted gait between January 2007 to December 2017. Local Ethics committee approved the study and written informed consent was not collectable from all patients since part of them was no longer attending the rehabilitation clinics. The STROBE guidelines were used to ensure a proper reporting of this observational study (Von Elm et al., 2008).

Subjects

The inclusion criteria for the study were: male or female older than 18years, with gait impairment due to an ischemic or hemorrhagic stroke occurred within 6 months from the onset. A set of demographic, clinical and functional parameters were retrospectively collected from digital medical records: i) age; ii) sex; iii) time since stroke; iv) Functional Independence measure (FIM): total score FIM (tFIM), motor subscore FIM (mFIM), and cognitive subscore FIM (cFIM) at admission and discharge; v) Functional Ambulatory Category at admission and discharge. In addition, we considereda set of measures related to the rehabilitation training protocol: i) length of rehabilitation stay (LOS); ii) number of RAGT sessions; iii) time since stroke event to rehabilitation.

The patients with severe anomalies of lower limbs (osteoporosis, skin injuries, and aggressive behaviour) and those who had any adverse event related to use Lokomat were excluded before or during RAGT training.

We evaluated the effect of sessions RAGT with exoskeleton Lokomat in multidisciplinary rehabilitation by their MCID set for FIM on the basis of the difference between imput and discharge FIM score and FAC admission and in demission. The MCID set for FIM is defined on the basis of the difference between the admission and discharge FIM score considering 22 points for the global FIM, 17 points for the motor FIM and 3 points for the cognitive FIM as MCID (Beninato et al. 2006). FIM is an appropriate measure, used in post-stroke patient on admission and discharge in rehabilitation (Brown et al. 2015). This clinical approach makes possible to determine improvement; and its specificity is based on the analysis of the patient's synthetic data, on his residual abilities and to those acquired (Sangha H et al. 2005).

We established and stratified according to the number of sessions received (sessions ≥14 and sessions < 14), demographic and clinical parameters the proportion of good responders (GR) as well as that of independent patients at the end of the rehabilitation program. At admission participants were defined by FAC scale between 0-3 because assisted either physically and or verbally (Smith M C et al 2017). The ability to walk independently is defined by FAC ≥ 4 (no physical and or verbal) assistance is the goal rehabilitation post stroke (Akulwar et al. 2019, Viosca E et al 2005). FAC is an instrument which has proved to be reliable and valid for the classification of the level of gait of patients after stroke. This instrument distinguishes among 6 levels ranging from dependence to independence (Perry J et al. 1995); in this study, it was assessed at admission of rehabilitation and then again at discharge.

Interventions

All patients received robot-assisted gait rehabilitation with a robotic exoskeleton system Lokomat (Hocoma Switzerland) that can guide hip and knee flexion through braces connecting the patient's legs to the machine. It also provides body weight support (0-100%) through a harness along with the level of assistance provided by the device. The entire device (including the harness and the motorized exoskeleton orthoses) can be adjusted according to the requirements of the process of treadmill rehabilitation. Motorized exoskeleton orthoses have a biomechanical role, which is to guide movements at the hips and knees that mimic a physiological gait pattern (Riener et al., 2010). Parameters are defined based on the functional characteristics of the patient, starting with a 50% reduction in body weight and 100% of the guidance provided by the robot. Over the sessions, adjustments can be made in increments or decrements of 10%. The RAGT session last approximately 45 minutes to an hour, including patient preparation. The treadmill speed can vary from 0.1 to 3 km/h (Mehrholz J et al. 2017; ARTIC 2018). In addition to RAGT, patients benefited from a multidisciplinary rehabilitation programme.

Multidisciplinary rehabilitation

A multidisciplinary programme is defined according to each individual's needs (conventional motor rehabilitation, occupational therapy, speech therapy and cognitive rehabilitation). For this reason intervention cannot be the same for all patients. The program considers specificities for each patient relating to his disability and for these circumstances different professional qualifications are required. Multidisciplinary can be exercised individually or collectively; however with objectives well targeted for each patient. At the admission, patient was assessed by a rehabilitation team who defined a specific program according to the framework of the international classification of functions of WHO (Lexell et al. 20014); and at discharge, a clinical evaluation was made to determine the functional improvement of patients (Lexell et al., 2014; Silva et al., 2015).

Statistic analysis

The data distribution was verified with the Shapiro-Wilk test.

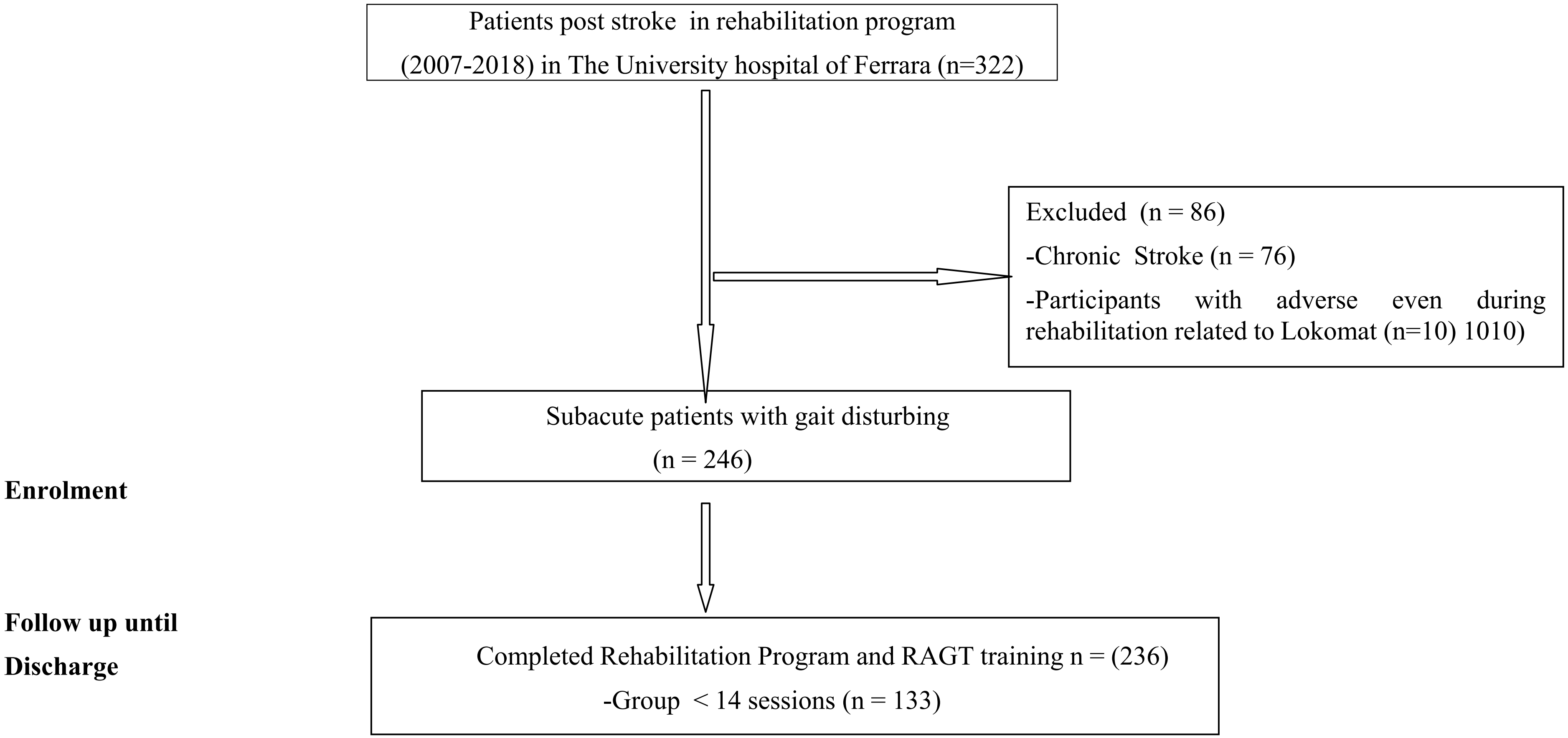
The baseline comparison between the groups was obtained through a chi-squared test for categorical variables, or an independent samples t-test or Mann-Whitney test for continuous variables. Within-group comparison was performed via paired sample t-tests or wilcoxon tests and between-group comparisons for all outcomes were obtained again with independent sample t-test or Mann-Whitney test according to data distribution. Multivariate and logistic regression models were employed to determine the impact on the FIM scale variations and on gait independence (FAC score >4). When needed, independent variable were opportunely dichotomized as follows: age (≤60 years), length of stay (≥100 days), RAGT sessions (≥ 14), days since stroke (≤ 6 weeks), stroke location and hemisphere.

A p value < 0.05 was considered statistically significant. Data analyses were performed with MedCalc software version 19.2 (MedCalc Software LtD. Ostend, Belgium

Results

322 patients with stroke that underwent a RAGT during a multidisciplinary rehabilitation program at University Hospital of Ferrara were assessed. Eighty-six patients were excluded because they did not meet the inclusion criteria. Specifically we excluded patients with chronic stroke (n=76), and those who interrupted RAGT training for medical condition (n=10) (See figure 13)

Figure 13: STROBE flow chart.



STROBE, Strengthening the Reporting of the Observational Study of RAGT's dose necessary in a multidisciplinary program of rehabilitation

Sample characteristics

We included 236 participants with a mean age of 62.73±11.82 year old; 91 (38.44%) were female and 145 (61.44%) were male. We highlighted a peak in the distribution for age at 60-70 years that represented the 33.4% of the entire population: whereas, only 25% of the sample was older than 75years. Ischemic stroke were 140 (59.32%) and hemorrhagic 96 (40.68%). The analyzed patients spent an average of 105.49 ± 58.88 days in the inpatient rehabilitation units.

Ischemic and hemorrhagic stroke differed for age, time since stroke, LOS, FIM total and cognitive score at admission. Specifically, hemorrhagic patients were younger (p=0.019) received rehabilitation later (p=0.013) and had a lower FIM score at admission (p=0.005) especially the cognitive domain (p=0.001) (See table 6).

Table 6: Sample characteristics

	Ischemic stroke n=140 (59.32%)	Hemorrhagic stroke n=96 (40.68%)	Total (n=236)	P value
Age, years	64.22 ± 11.83	60.55 ± 11.52	62.73 ± 11.82	0.019
Male sex, n (%)	87 (62.14%)	58 (60.42%)	145 (61.44%)	0.78
Time since stroke (days)	45.49 ± 38.56	59.22 ± 45.57	51.08 ± 42.01	0.013
Stroke location:				
subcortical	46 (32.90%)	54 (56.20%)	100 (42.40%)	0.42
cortical-subcortical	63 (45.00%)	30 (31.20%)	93 (39.40%)	<0.001
cortical	11 (7.90%)	3 (3.10%)	14 (5.90%)	0.033
brainstem	17 (12.10%)	7 (7.30%)	24 (10.20%)	0.041
cerebellar	3 (2.10%)	2 (2.10%)	5 (2.10%)	0.65
Side lesion:				
Right hemisphere	73 (52.10%)	38 (39.60%)	111 (47.00%)	0.009
Left hemisphere	67 (47.90%)	58 (60.40%)	125 (53.00%)	0.42
LOS (days)	95.05 ± 53.97	120.71 ± 62.60	105.49 ± 58.88	0.001
FAC at admission	0.43 ± 0.73	0.26 ± 0.58	0.36 ± 0.68	0.07
tFIM at admission	48.89 ± 18.10	41.79 ± 19.90	46.00 ± 19.13	0.005
mFIM at admission	25.63 ± 11.81	22.70 ± 11.30	24.44 ± 11.66	0.06
cFIM at admission	23.61 ± 8.81	19.22 ± 10.44	21.82 ± 9.73	0.001

LOS: Length of Stay; FAC: Functional Ambulatory Category; FIM: Functional Independence Measure.

Each participant included in this study completed at least 7 RAGT sessions, with a median value of 13 sessions (interquartile range 7-21), without any adverse event related to the training. Training lasted a median of 44 (28-71) days, with a mean number of 2.1 ± 0.6 sessions per week (median 2 IQR 1.6-2.5).

After rehabilitation, all patients improved respect to baseline ($p<0.001$) without any differences among different type of stroke except for the cognitive domain ($p=0.020$) (see table 7).

Table 7: Clinical Outcome after RAGT training

	Ischemic stroke (n=140)			Hemorragic stroke (n=96)			
	Baseline	Discharge	P value	Baseline	Discharge	P value	Between-group p value
mFIM	25.63 ± 11.81	55.37 ± 19.17	<0.001	22.70 ± 11.30	51.01 ± 20.65	<0.001	0.51
cFIM	23.61 ± 8.81	29.27 ± 5.81	<0.001	19.22 ± 10.44	26.95 ± 8.06	<0.001	0.020
tFIM	48.89 ± 18.10	84.44 ± 22.17	<0.001	41.79 ± 19.90	77.96 ± 27.02	<0.001	0.81
FAC	0.43 ± 0.73	2.41 ± 1.31	<0.001	0.26 ± 0.58	2.16 ± 1.32	<0.001	0.60

Predictors of functional recovery

Linear regression models highlighted predictive effects of some variables on functional independence. For total FIM score, a significant model ($R^2 = 0.26$ $p < 0.001$) included age, baseline total FIM score and time since stroke.

For motor FIM score a similar significant model was observed ($R^2 = 0.25$ $p< 0.001$) that included age, baseline motor FIM score and time since stroke.

For cognitive FIM score a fitting model was observed (R2 = 0.565 p= < 0.001) that only included baseline cognitive FIM score and time since stroke.

A logistic regression model predicted the chance to become independent at discharge from rehabilitation, reaching a FAC level (Smith et al., 2017). It was significant ($R^2 = 0.30$ $p < 0.001$) and included age < 60 (OR: 5.43 95% CI 2,44-12.11) and baseline total FIM score > 40 (OR: 7.27 95%CI 3.34-15.83).

Considering the MCID value described by Beninato et al. (Beninato 2006), we categorize our sample in good responders and poor responders revealing how the 74.57% was considered good responders for total FIM, 74.15% for FIM motor domain and 62.25% for FIM cognitive domain.

Next, we evaluated the differences in the % of responders respect to RAGT dose, age and time since stroke, confirming the positive effects of these factors on functional recovery. Patients that received at least 14 RAGT sessions, had 15.83% more chance to be responders compared to those that receive less sessions ($p=0.006$). Similarly, younger patients (≤60 years) were more prone to be responders (+15.1%). Lastly, an early rehabilitation was found to be more efficient (+21.09%) in determining responsiveness ($p < 0.001$).

Becoming newly independent for gait, that refers to a FAC score ≥ 4, was related only with age ($p=0.001$) (see table 8).

Table 8: Factors influencing functional recovery after RAGT (dose, age, time since stroke)

	≥14 sessions n=(103)	<14 sessions (n=133)	p value	< 60 years old (n=88)	≥ 60 years old (n=148)	P value	<6weeks (n=138)	≥6weeks (n=98)	P value	Total (n=236)
tFIM GR, n (%)	86 (83.5%)	90 (67.67%)	0.006	74 (84.1%)	102 (68.9%)	0.010	115 (83.33%)	61 (62.24%)	<0.001	176 (74.58%)
mFIM GR, n (%)	83 (80.58%)	92 (69.17%)	0.048	71 (80.68%)	104 (70.28%)	0.08	114 (82.61%)	61 (62.24%)	<0.001	175 (74.15%)
cFIM GR, n (%)	75 (72.82%)	79 (59.4%)	0.032	65 (73.86%)	89 (60.13%)	0.033	90 (65.22%)	64 (65.31%)	0.99	154 (65.25%)
Newly Independent,n (%)	15 (14.56%)	30 (22.56%)	0.13	27 (30.68%)	18 (12.16%)	< 0.001	31 (22.46%)	14 (14.29%)	0.12	45 (19.07%)

GR= good responder

Discussion

Over the past two decades, robotic-assisted gait training (RAGT) has been introduced in clinical practice as a valuable option to increase training intensity and foster functional recovery in patients with stroke (Hidler J et al 2011; Fazekas G et al 2019).Thus, international guidelines for stroke management recommended its use for patients with severe gait impairments (Winstein et al 2017; Schwartz et al . 2009). In this pragmatic study, we explored the role of RAGT dose on functional recovery in a large cohort of patients with stroke and dependent walking. Our sample characteristics were similar to other pragmatic studies (ARTIC 2018) where patients with stroke that received RAGT were usually younger than the age when stroke more often occurs (Roy-O'Reilly et al 2018; Kelly-Hayes et al 2010) and with a higher % of hemorrhagic stroke (40%) compared with the worldwide representation (Feigin 2015). This can be explain by the fact that hemorrhagic stroke usually are severe with motor and cognitive deficits (Appelros p et al 2007; Elwood D et al. 2009). In our cohort, compared with ischemic stroke, hemorrhagic patients were younger, started rehabilitation later, had longer rehabilitation length of stay and were more impaired at admission, above all respect to cognition. Length of stay reflects both stroke severity, presence of comorbidities but also social and personal factors (Miyoshi S et al 2018, Morone et al 2018).However, both type of stroke recovered in the same manner, without any differences, as previously reported (Dierick 2018). Our pragmatic study confirmed several factors that can be determinant for functional recovery after stroke: age, time since stroke and the intensity of training.

In our sample, 37.3% of patients had <60 years and they significantly recovered more after rehabilitation with greater chance to be newly gait independent at discharge. This findings confirmed the hypothesis that a younger age is related with a better outcome (Roy-O' Reilly et al 2018; Lui SK et al 2018; Xue Long et al 2016; Palnum KD et al 2008; Bagg S et al 2002).

Similarly, we found higher functional gains in patients that received RAGT earlier (within 6 weeks). Indeed, a specific time-window for spontaneous recovery exists, that can be set within the first 6-12 weeks for gait recovery (Smith 2017; Nilsson, A. E al 2014; Björn R et al. 2016), when gait robotics are recommended to optimize functional gains (Mehrholz et al. 2017).

Regarding RAGT training intensity, defined by the rehabilitation time, in our sample a wide range of training sessions was reported (between 7 to 21). However, a minimum of 14 RAGT sessions have been set to obtain a favourable outcome at discharge. This value is slightly lower that the 16-18 sessions reported by the ARTIC network (ARTIC 2018). We should bear in mind that other parameters of training (i.e. velocity, guidance, body-weight support, heart rate, perceived exertion) should be considered when exploring the dose-response relationship of RAGT training. The importance on intensity in stroke gait rehabilitation has been elegantly proved by Klassen et al. (Klassen 2020) that confirmed how higher doses of training determined long-lasting functional effects in subacute stroke patients.

This pragmatic study was a unique opportunity to open a window on the use of robot-assisted gait training into clinical practice for stroke survivors, overcoming the limited generalizability of the clinical randomized controlled trials. However, several limitations have to be taken into account. Firstly, we cannot establish a direct cause-effect relationship between the analyzed factors (RAGT dose, age and time since stroke); the retrospective nature of the study limited the availability of the clinical data.

Conclusion

Patients with stroke (ischemic and hemorrhagic) reported similar recovery after a multidisciplinary rehabilitation that included a robot-assisted gait training program. An higher dose of RAGT (> 14 sessions), as well as a younger age (< 60 years old) and an early rehabilitation (< 6 weeks since stroke) are determinant factors of favourable recovery. However, only age seems to influence the chance to be a newly independent walker at discharge.

REFERENCES

Akulwar IS, Somaiya KJ. Impact of Cognitive Impairments on Functional Ambulation in Stroke Patients. Int J Phys Med Rehabil. 2019; 7(5) an open access journal ISSN: 2329-90.
Appelros P. Prediction of Length of Stay for Stroke Patients. Acta Neurol Scand. 2007; 6(1):15-9. DOI: 10.1111/j.1600-0404.2006.00756.x.

Bagg S, Pombo AP, and Hopman Wilma. Effect of Age on Functional Outcomes After Stroke Rehabilitation. Stroke. 2002; 33(1):179–185. Doi:org/10.1161/hs0102.101224.

Beninato M, Gill-Body KM, Salles S, Stark PC, Black-Schaffer RM, Stein J. Determination of the minimal clinically important difference in the FIM instrument in patients with stroke. Arch Phys Med Rehabil. 2006; 87(1):32-9. DOI: 10.1016/j.apmr.2005.08.130.

Björn R., Gumbinger, C, Sauer T, Wiethölter H, Bruder I, Diehm C, Ringleb PA, Hacke W, Hennerici MG, Kern Rolf, and Stroke working group of Baden- Wuerttemberg. Access, timing and frequency of very early stroke rehabilitation – insights from the Baden-Wuerttemberg stroke registry. BMC Neurol. 2016; Art ID 222.
https://doi.org/10.1186/s12883-016-0744-7.

Bradley Hobbs and Panagiotis Artemiadis. A Review of Robot-Assisted Lower-Limb Stroke Therapy: Unexplored Paths and Future Directions in Gait Rehabilitation. Front Neurorobotic. 2020 ; 14(19). Doi: 10.3389/fnbot.2020.00019

Brown, A W; Therneau T M; Schultz B A ; Niewczyk P M; Granger CV; Measure of Functional Independence Dominates Discharge Outcome Prediction After Inpatient Rehabilitation for Stroke. Stroke. AHA journal. 2015; 46:1038-1044. DOI: 10.1161/STROKEAHA.114.007392.

Conesa L, Costa U, Morales E, Edwards DJ, Cortes M, Leon D, Bernabeu M &Medina J. An observational report of intensive robotic and manual gait training in subacute stoke. 2012. J Neuroeng Rehabil, 9, 13,

Dierick F, Dehas M, Isambert JL, Injeyan S, Bouche AF, Bleyenheuft Y & Portnoy S. Hemorrhagic versus ischemic stroke: Who can best benefit from blended conventional physiotherapy with robotic-assisted gait therapy? Plos One. 2017: 12(6):e0178636

Duncan P W, Sullivan K J, Behrman A L, et al. Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011; 364(21): 2026-2036. Doi: 10.1056/NEJMoa1010790.

Elwood D , Rashbaum I, Bonder J et al. Length of Stay in Rehabilitation is Associated With Admission Neurologic Deficit and Discharge Destination.
PM&R; 1(2):147-51. DOI: 10.1016/j.pmrj.2008.10.010.

Eng JJ, Pei Fang Tang. Gait training strategies to optimize walking ability in people with stroke: A synthesis of the evidence. Expert Rev Neurother. 2007 7(10): 1417–1436.doi: 10.1586/14737175.7.10.1417.

Fazekas G & Tavaszi I. The future role of robots in neuro-rehabilitation. Expert Review of Neurotherapeutics. 2019 ;19(6): 471-473. doi.org/10.1080/14737175.2019.1617700.

Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, Barker Collo S ,Moran AE, Sacco RL,Truelsen T. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015; 45: 161-176.doi.org/10.1159/000441085.

Heshmatollah A, Mutlu U, Koudstaal PJ. et al. Cognitive and physical impairment and the risk of stroke – A prospective cohort study. Sci Rep. 2020; 10, 6274. https://doi.org/10.1038/s41598-020-63295-y.

Hidler J, Diane Nichols, Marlena Pelliccio, Kathy Brady, Donielle D, Campbell JH, Kahn T, Hornby G. Multicenter Randomized Clinical Trial Evaluating the Effectiveness of the Lokomat in Subacute Stroke. Neuroreabilitation and Neural repair. 2009; 23(1): 5-13 https://doi.org/10.1177/1545968308326632.

Kelly-Hayes M. Influence of Age and Health Behaviours on Stroke Risk: Lessons from Longitudinal Studies.J Am Geriatric Soc. 2010. 58 (Suppl 2): S325–S328.Doi: 10.1111/j.1532-5415.2010.02915.x

Kim J, Thayabaranathan T, Donnan GA, Howard G, Howard VJ, Rothwell PM, Feigin V, Norrving BO, Owolabi M, Pandian J et al. Global Stroke Statistics 2019. Int J Stroke. 2020; 15(8):819-838.doi.org/10.1177/1747493020909545.

Klassen TD, Dukelow SP, Bayley MT, Benavente O, Hill MD, Krassioukov A, Liu-Ambrose T, Pooyania S, Poulin MJ, Schneeberg A, Yao J, Eng JJ. Higher Doses Improve Walking Recovery During Stroke Inpatient Rehabilitation. Stroke. 2020; 51(9): 2639-2648. doi: 10.1161/STROKEAHA.120.029245.

Lexell J, Brogardh C. The use of ICF in the neurorehabilitation process. Neurorehabilitation. 2014; 36(1). DOI: 10.3233/NRE-141184. Source: PubMed.

Lohse KR, Lang CE, Boyd LA. Is better? Using metadata to explore dose-response relationships in stroke rehabilitation.Stroke.2014;45(7):2053-8.Doi: 10.1161/STROKEAHA.114.004695.

Lui SK, Ha Nguyen M. Elderly Stroke Rehabilitation: Overcoming the Complications and Its Associated Challenges. Curr Gerontol Geriatr Res.2018; art ID 9853837 Doi: 10.1155/2018/9853837.

Mehrholz J, Thomas S, Werner C et al. Electromechanical-Assisted Training for Walking After Stroke. Cochrane data base syst Rev. 2017 ; 5(5). Doi: 10.1002/14651858.CD006185. pub 4.

Miyoshi S & Shinohara A. Reducing Length of Stay in Rehabilitation Hospital after Stroke by Refining the Rehabilitation Program. Rehabilitation Science. 2018; 3(4) : 54-58. doi: 10.11648/j.rs.20180304.11.

Morone G, Massiero S, Coiro P, De Angelis D, Venturiero V, Paolucci S & Tosa M. Clinical features of patients who might benefit more from walking walking robotic training. J restorative neurology and neurosciences. 2018; 36(2): 293-299. DOI: 10.3233/RNN-170799.

Nilsson A, Vreede KS, Häglund V. *et al.* Gait training early after stroke with a new exoskeleton – the hybrid assistive limb: a study of safety and feasibility. J NeuroEngineering Rehabil. 2014; 2014. 11(92). https://doi.org/10.1186/1743-0003-11-92.

Palnum KD, Petersen P, Sørensen HT, Ingeman A, Mainz J, Bartels P, Johnsen SP. Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nation wide follow-up study.Age and Ageing. 2008; 37(1): 90-5. Doi: 10.1093/ageing/afm134.

Pennycott A, Wyss D, Heike V, Klamroth-Margansk V, Riener R. Towards more effective robotic gait training for stroke rehabilitation: Journal of NeuroEngineering and Rehabilitation. A review. 2012; 9 (1). Article number 65. Doi.10.1186/1743-0003-9-65.

Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of Walking Handicap in the Stroke Population. Stroke. 1995; 26 (6): 982-989 https://doi.org/10.1161/01.STR.26.6.982Stroke.

Poli P, Morone G, Rosati G and Masiero S. Robotic Technologies and Rehabilitation: New Tools for Stroke Patients' Therapy. BioMed Research International. 2013; 2013 art number 153872. https://doi.org/10.1155/2013/153872.

Riener R, Lùnenburger L, Maier IC, Colombo G, Dietz V. Locomotor training in subjects with sensory-motor deficit: an overview of robotic gait orthosis Lokomat. Health care engineering. 2010; 1(2): 197-216. doi: 10.1260/2040-2295.1.2.197.

.

Riener R. Technology of the Robotic Gait Orthosis Lokomat. Neurorehabilitation Technology.2016;395-407.2nd edition.Springer International Publishing. Doi.org/10.1007/978-3-319-28603-7_19.

Roy-O'Reilly M, McCullough LD. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. Endocrinology. 2018. 159(8): 3120–3131. Doi:org/10.1210/en.2018-00465.

Sangha H, Lipson D, Foley N et al. A comparison of the Barthel Index and the Functional Independence Measure as outcome measures in stroke rehabilitation: patterns of disability scale usage in clinical trials. Int J Rehabil Res. 2005; 28(2):135-139. DOI: 10.1097/00004356-200506000-00006.

Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, Meiner Z. The Effectiveness of Locomotor Therapy Using Robotic-Assisted Gait Training in Subacute Stroke Patients: A Randomized Controlled Trial.PM&R. 2009.1(6): 516-523. https://doi.org/10.1016/j.pmrj.2009.03.009.

Sheng Li, Gerard EFand Ping Zhou. Post-stroke Hemiplegic Gait: New Perspective and Insights. Font Physiol. 2018; https://doi.org/10.3389/fphys.2018.01021.

Silva SM, Correa FI, De Morais Faria CDC, Buchalla CM, Da Costa Silva PF, Correa JCF. Evaluation of post-stroke functionality based on the International Classification of Functioning, Disability, and Health: a proposal for use of assessment tools. J Phys Ther Sci. 2015; 27(6): 1665–1670. Doi: 10.1589/jpts.27.1665.

Smith M-C, Barber PA, and Stinear C M. The TWIST Algorithm Predicts Time to Walking Independently After Stroke. Neurorehabilitation and Neural Repair. 2017; 31(10-11): 955–964. DOI: 10.1177/1545968317736820.

Straudi S, Severini G, Da Roit M, Pizzongolo LDM, Martinuzi C, Basaglia N. The dose of robot-assisted gait therapy may influence functional recovery in a multidisciplinary rehabilitation program: an exploratory restrospective study. Int J Rehabil Res. 2020; 43(2): 75-182. Doi 10.1097MRR0000000000000407.

Van Hedel1 H J A, Severini G, Scarton A, et al. ARTIC (Advanced Robotic Therapy Integrated Centres): An International collaboration facilitating the application of rehabilitation technologies. Journal neuroengineering and rehabilitation. 2018; 15(30). Doi: 10.1186/s12984-018-0366-y.

Viosca E, Martinez JL, Almagro PL, Gracia A, Gonzales C. Proposal and Validation of a New Functional Ambulation Classification Scale for Clinical Use. Ach PM&R. 2005, 86 (6) 1234-1238. https://doi.org/10.1016/j.apmr.2004.11.016.

von Elm E, Altman DG , Egger M, Pocock SJ , Gøtzsche PC, Vandenbroucke JP, and for the STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: for reporting observational studies. Bull World Health Organ. 2007; 85(11): 867–872. doi: 10.2471/BLT.07.045120.

Warraich Z and Kleim JA.N eural plasticity: the biological substrate for neurorehabilitation.PM&R. 2010;2(12Suppl2):S208-19. DOI: 10.1016/j.pmrj.2010.10.016.

Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016; 47(6): :e98-e169. doi: 10.1161/STR.0000000000000098.

Xue Long,Yongzhong Lou, Hongfei Gu, Xiaofei Guo et al. Mortality, Recurrence, and Dependency Rates Are Higher after Acute Ischemic Stroke in Elderly Patients with Diabetes Compared to Younger Patients. Front Aging Neurosci. 2016; 8(142). Doi. 10.3389/fnagi.2016.00142.

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3. CONCLUSION

In my thesis, I explored the main determinants of recovery after RAGT training within a multidisciplinary program in a cohort of severe traumatic brain injury and subacute stroke patients. In addition to the RAGT, patients benefited from a program defined on individual needs (conventional motor rehabilitation, occupational therapy, language and cognitive rehabilitation).

The main objective of this retrospective study was to assess the possible association between the parameters linked to the treatment of robot-assisted walking (number of sessions, frequency, LOS, etc.) in patients suffering from brain injury and the functional recovery obtained at discharge of the multidisciplinary rehabilitation program measured by the FIM (total), FAC and LCF scores.

The evidence on robotic gait rehabilitation are sometimes mixed, with some pointing to the additional effectiveness of using RAGT over traditional rehabilitation. It has been proven an increase in the performance of the 6-minute walk test after use of Lokomat versus conventional equivalent-time (hourly) rehabilitation (Goffredo et al. 2019, Bruni et al. 2018, Mayr et al. 2007). However, experiments with stroke patients found no improvement in walking speed after using RAGT at less than 3 months (Combs-Miller et al. 2014, Schwart et al 2009). Hidler et al. (2009) and Combs-Miller et al. (2014) demonstrated that with RAGT there was no improvement in the spatio-temporal parameters of walking compared to conventional rehabilitation. Other studies, on the other hand, have revealed that there is no significant difference in the spatio-temporal parameters between the two practices (Goffredo et al. 2019).

Cortical reorganization being motivated by neuronal plasticity not seems to be only the process of brain plasticity. Regarding this report, it is important to consider both the plasticity process as a whole, and the reorganization that could in particular lead to functional recovery as revealed by different neurophysiological and neuroimaging techniques (TMS, fNIRS, fMRI, EEG). The process of adaptive plasticity consits of brain connection reorganization, retructuration of existing neural connections or a formation of new neural connections with the aim of restoring partialy or totaly cognitive or behavioral functions and motor lost during a traumatic event.

However, the process of adaptability of patients after a multidisciplinary rehabilitation program that encompasses RAGT has been positive revealed (Moucheboeuf G et al. 2020, Morone G et al.2017, Dundar et al. 2014, Mehlrolz et al. 2013).

Age remains one of the undeniable characteristics that conditions brain plasticity (Black-Schaffer et al. 2004, Bagg et al. 2002). The work of Margaret Kennard (1942) led to her eponymous principle that injuries early in life resulted in better healing than injuries that occurred later, this observation remains relevant today. Likewise, the advantage of spontaneous recovery is not to be overlooked. It occurs early in the recovery process and depends largely on the age and past time before rehabilitation. In contrast, induced recovery is a result of the training process occurring within the context of rehabilitation experience and efforts. The process may continue to occur long after the spontaneous processes have ceased.

Our study like other reports indicated that the most dramatic improvements occur within the first 6 weeks, if not at the shortest scales (Verheyden et al. 2008, Kwakkel et al. 2006, Kollen B et al 2005). Regarding the spontaneous recovery period, some plasticity studies subdivide post-injury recovery into several semi-overlapping epochs (Belagaje et al. 2010, Cramer 2008).

3.1 References

Bagg S, Pombo AP, and Hopman W. Effect of Age on Functional Outcomes After Stroke Rehabilitation. Stroke. 2002; 33(1):179–185. Doi:org/10.1161/hs0102.101224.

Belagaje S and Kissela B. Epidemiology of stroke recovery. In S. Cramer and Nudo (Eds.) Brain Repair After Stroke. 2010; 163-172. Cambridge: Cambridge University Press. Doi:10.1017/CBO9780511777547.016.

Black-Schaffer RM , Cynthia Winston. Age and Functional Outcome After Stroke. Top Stroke Rehabil. 2004; 11(2):23-32. DOI: 10.1310/DNJU-9VUH-BXU2-DJYU.

Bruni MF, Melegari C, De Cola MC, Bramanti A, Bramanti P& Calabrò RS. What does best evidence tell us about robotic gait rehabilitation in stroke patients: A systematic review and meta-analysis. J clinical Neuroscience. 2018; 48: 11-17. https://doi.org/10.1016/j.jocn.2017.10.048.

Cramer ST. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. Annals of Neurology. 2008. https://doi.org/10.1002/ana.21393.

Combs-Miller SA, Kalpathi Parameswaran A, Colburn D, Ertel T, Harmeyer A, Tucker L, Schmid AA. Body weight supported treadmill training vs. overground walking training for persons with chronic stroke: a pilot randomized controlled trial. Clin Rehabil. 2014; 28(9):873–884. DOI: 10.1177/0269215514520773.

Dundar U, Toktas H, Solak O, Ulasli AM & Eroglu S. A Comparative Study of Conventional Physiotherapy Versus Robotic Training Combined with Physiotherapy in Patients with Stroke. Topics in Stroke Rehabilitation. 2014; 21(6), 453-461. DOI: 10.1310/tsr2106-453.

Goffredo M , Iacovelli C , Russo E , Pournajaf S, Di Blasi C, Galafate D, Pellicciari , Agosti M , Filoni S, Aprile I and Franceschini M. Stroke Gait Rehabilitation: A Comparison of End-Effector, Overground Exoskeleton, and Conventional Gait Training. Applied Sciences.2019; 9: 26-27. Doi:10.3390/app9132627.

Hidler J, Nichols D, Peliccio M, Brady K, campbell DD, Kahn JH et al. Multicenter randomized clinical trial evaluating the effectiveness of the lokomat i subacute stroke. Neurorehabil Neural Repair. 2009; 23(1): 5-13.

Kollen B, Van de Port I, Linderman E, Twisk J and Kwakkel G. Predicting improvement in gait after stroke: a longitudinal prospective study. Stroke. 2005; 36(12): 2676-80. DOI: 10.1161/01.STR.0000190839.29234.50.

Kwakkel G, Kollen B and Twisk J. Impact of time on improvement of outcome after stroke. Stroke. 2006; 37(9): 2348-53. Doi: 10.1161/01.STR.0000238594.91938.1e.

Mayr A, Kofter M, Qirbach E, Matzak H, Fròhlich K, Saltuari L. Prospective blinded, randomized crossover study of gait rehabilitation in stroke patients using the lLokomat gait orthosis. Neurorhabil Neural Repair. 2007; 21(4): 307-314.

Mehrholz J, Elser B werner C, Kugler J, Pohl M. Electromechanical-asisted training for walking after stroke. Cochrane Database Syst Rev. 2013; 7: CD006185.

Morone G, Paolucci S, Cherubini A, De Angelis D, Venturiero V, Coiro P and Iosa M. Robot-assisted gait training for stroke patients: current state of the art and perspectives of robotics. Neuropsychiatr Dis Treat. 2017; 13: 1303-1311. Doi: 10.2147/NDT.S114102

Moucheboeuf G, Griffier R, Gasq D, Glize B, Bouyer L, Dehall P, Casoudesalle H. Effects of robotic gait training after stroke: A meta-analysis. Annals of Physical and Rehabilitation Medicine. 2020; 63(6): 518-534. https://doi.org/10.1016/j.rehab.2020.02.008.

Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, et al. The effectiveness of locomotor therapy using robotic-assisted gait trainng in subacute stroke patients: a randomized conroled trial. PM&R. 2009; 1 (6): 516-523.

Verheyden G, Nieuwboer A, De Wit L, Thijs V, Dobbelaere J, Devos H, Severlijns D, Vanbeveren S, De Weetdt W. Time course of trunk, arm, leg, and functional recovery after ischemic stroke. Neurorehabil Neural Repair. 2008; 22(2): 173-179. DOI: 10.1177/1545968307305456

4. CONGRESS PUBLICATIONS

13th World Congress on Brain Injury
March 13-16 2019 Toronto Canada
(International Brain Injury
Association's) Pulished oline 05
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[0365] The impact of the cognitive level on recovery in traumatic brain injury patients during a robot-assisted gaittraining (RAGT). An exploratory retrospective study.

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Abstract

Background: Traumatic brain injury (TBI) leads to cognitive and functional sequelae in 25-95%. Recently, robot-assisted gait training (RAGT) has been introduced in the rehabilitation settings to increase functional recovery; however, no clear evidence is available on the role of the cognitive status on the applicability and effects of this intervention.

The aim of this study was to investigate the role of the cognitive level at admission on recovery, in terms of walking function, independence of daily living and cognition, in a cohort of TBI patients who received RAGT.

Methods

We retrospectively analyzed a database that includes patients with TBI who undergone an inpatient multidisciplinary rehabilitation at Ferrara University Hospital and received a robot-assisted gait rehabilitation (Lokomat, Hocoma, Switzerland) between January 2007 and December 2017. In this retrospective observational study, we have collected demographic (sex, age) and clinical data. Moreover, a set of outcome measures at admission and discharge has been registered to measure their walking function (Functional Ambulatory Classification), independence of daily living (Functional Independence Measure) and cognition (Levels of Cognitive Functioning). In addition, the rehabilitation length of stay (LOS) and the number of RAGT sessions were collected.

Results

We collected 86 patients with TBI (20 females and 66 males, 34.96 ± 16.11 years, 15- 8979 days since TBI) who underwent RAGT during their rehabilitation. They were grouped into three classes according to their level of cognitive functioning (LCF); group 1 LCF 2-3(n = 26); group 2 LCF 4-5 (n=27); group 3 LCF 6-7 (n = 33). The analysis showed that patients with a low cognitive level at admission had the greater recovery during rehabilitation, characterized by an improvement not only of their cognition ($p = 0.001$), but also of their walking function ($p = 0.037$) and independence of daily living ($p = 0.0001$). In addition, evidence of greater gains were demonstrated in patients in the sub-acute rather than chronic rehabilitation phase ($p = 0.0001$). All groups received the same number of RAGT sessions during rehabilitation.

Conclusion

A classification based on the level of cognition at admission highlighted the proportional recovery reached by TBI patients during a multidisciplinary rehabilitation that encompass robot-assisted gait training.

Key words: cognition, chronic, sub acute, rehabilitation

POSTER

Introduction

The rehabilitation in training in gait with "Lokomat Hocoma" Switzerland" have impact in motor recovery in TBIis commonly accepted, but his possibility to improve the cognitive level is not available in litterature or at least it is speak little about it
However, this study highlight the improvement of level of consciousness evaluated in scale of level of cognitive function(LCF) after gait rehabilitation by "Lokomat Hocoma" within a multidisciplinary rehabilitation.

Materials and Methods

The Lokomat as training for walking the robot:
-> Exoskeleton system ->
+Walking orthosis: - Guide the gait and the rhythm of step. .
-Adjustable according to size and templatepatient (Adult orthosis and orthotics for children)
*Adult: length of the femur is between 35 and 47 cm.
+ Compound system: --conveyor belt,
- weight support belt
- walking orthoses for both legs control functions.

-The devices are activated for the knee and hip joints.

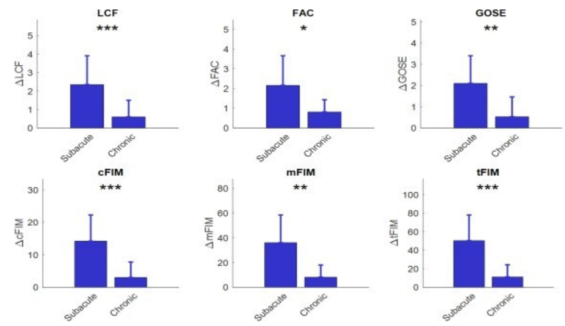
The observation consists to collect:
* outcomes of patients whom undergone RAGTwithin multidisciplinary rehabilitation.

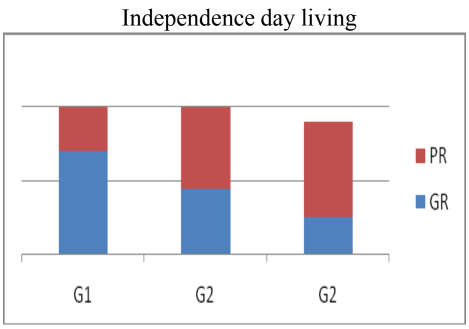
*Demographic (Gender, age)
* Clinical Outcomes **FAC** (Functional Ambulatory Classification), **FIM** (Functional Independence Measure), **LCF** (Level of cognitive functioning) at admission and discharge and number of RAGT session
Patients were grouped into **three classes** according to th**eir level of consciouness (LCF)**:
-group 1 **LCF 2-3** (n = 27); - group 2 **LCF 4-5-6** (n=45); group **3 LCF 7-8** (n = 13).
Results have been then analyzed and **compared** with different **mathematical models** and **literature results**

Results

* Patients with a **low consciouness level** at admission had the **greater recovery** in their **consciousness level** during rehabilitation **(P=0,001).**

*The analyse for the same patients also shows a nice recovery of the **walking function (P=0,037)** and the **independence of day living (P=0, 0001). They have (G1 patients) a large proportion of Good responders** comparatively at patients of G2 and G3.
* Signs of **greater gains** have been demonstrated in **sub acute patients** rather than **chronic patients (P=0, 0001).**





Conclusion

A classification based on the level of cognition at admission highlighted the proportional recovery reached by TBI patients during a multidisciplinary rehabilitation that encompass robot-assisted gait training**.**

References:

-Esquenazi A & Al. Randomized Comparative Study of Manually Assisted Versus Robotic-Assisted Body Weight Supported Treadmill Training in Persons With a Traumatic Brain Injury. American Academy of Physical Medicine and Rehabilitation. 2013; 5(4): 280-290
- Lapitskaya N, & Al. Robotic gait training in patients with impaired consciousness due to severe traumatic brain injury. J

Brain Injury. 2011;25(11): 1070-79
-O'Brien A & al. Robotic-assisted Gait Training as Part of the Rehabilitation Program in Persons with Traumatic and Anoxic Brain Injury.PMR.2016; 97(10): e117.

LLO

APPENDIX

Publications related to the thesis

Scientific Publications

Lissom LO, Bonsangue V, Maca M, Lavezzi S, Severini G, Straudi S, Basaglia N. **The cognitive level does not interfere with recovery after robot-assisted gait training in Traumatic Brain Injury: A ten year cohort study.** 2021. Technology and Disabiity. Vol. Pre-press, n° Pre-press, pp 1-7. Doi: 10:3233/TAD-200324.

Lamberti N, Manfredini F, Lissom LO, Lavezzi S, Basaglia N, Straudi S. **Beneficial effects of robot-assisted gait training on functional recovery in women after stroke: a cohort study**. Manuscript ID: medicina-1405907 - Accepted for Publication. Journal MDPI. https://www.mdpi.com/journal/medicina/special_issues/Acute_Ischemic_Stroke.

Lissom LO, Lamberti N, Manfredini F,Lavezzi S, Basaglia N, Straudi S. **Is Robot-assisted Gait Training Intensit a Determinant of Functional Recovery Early after Stroke? A Pragmatic Observational Study of Clinical Care.** *Article originale Submitted* . IJRR. .

Congress publication

[0365] Macca M, Bonsangue V, Lissom L, Laxezzi S, Severini G, Straudi S, Basaglia N. **The impact of the cognitive level on recovery in traumatic brain injury patients during a robot-assisted gait training (RAGT). An exploratory retrospective study**. *International Brain Injury Association's 13th World Congress on Brain Injury. March 13 - 16, 2019 Toronto, Canada.y. 33:sup1, 1.337. DOI: 10.1080/02699052.2019.1608749.*