Recovery of walking ability using a robotic device

Michiel van Nunen

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INHOUDSOPGAVE

Chapter 1

General Introduction

INTRODUCTION

Neurological injuries, such as stroke and spinal cord injury often result in physical impairments that interfere with a person's ability to walk.[1] Loss of walking ability often creates dependency on a wheelchair or other assistive mobility devices like ankle foot orthoses or canes.[1] The ability to walk is an important prerequisite for the performance of many daily-life activities. For many people with neurological injuries, recovery of walking ability is one of the most important goals during rehabilitation and gait therapy is, therefore, a key component of the rehabilitation program for these persons.[2,3] In addition, walking ability largely contributes to the overall fitness level of the patient which in turn influences the health status of the patient.[4] As such, optimization of therapeutic methods/techniques to improve walking has received considerable attention during rehabilitation and in research. Several treatment approaches to re-learning motor function and performance have been used so far.[5] However, treatment outcomes are still not satisfactory in many cases and therefore, many scientists are studying how to best improve walking ability in neurological patients.

This introduction outlines the focus of this thesis: the recovery of walking ability using a robotic device. It shortly introduces two neurological injuries (stroke and spinal cord injury) that often have devastating influence on the lives of the individuals affected by the injury. Furthermore, this introduction will provide a very short history of the development of the concept of robot-assisted therapy. Finally, it will describe the questions addressed in this thesis.

Stroke

During stroke or cerebrovascular accident (CVA), brain cells get deprived of oxygen resulting in damage to the involved brain area. Deprivation of oxygen can be a result of disrupted blood circulation in the brain by either an obstruction in an artery (ischemia) or by a rupture of one of the blood vessels (hemorrhage) in the brain. As a consequence, the functions of the involved parts of the brain are impaired. For example, if brain areas involved in motor functions are damaged, this results in impairment of movements on the side contralateral to the side of the damage to the brain. Depending on the location and severity of the lesion, stroke may result in motor impairments, sensory impairments, balance problems, speech disorders, visual field defects and changes in cognitive and emotional functioning. Stroke is a leading cause of mortality and disability in the western world.[6] Presently, more than 35000 people in the Netherlands suffer from a first ever stroke each year[7] of whom almost 9000 die as a result of this stroke (shortly) after onset. For the survivors, as many as 80% initially loose walking skill.[8] Although substantial recovery from the initial

impairments is commonly observed in these patients, after 6 month of rehabilitation, half of the survivors still suffer from remaining impairments.[9]

Spinal cord injury

A variety of symptoms are associated with spinal cord injury (SCI), depending on the size and the location of the lesion. The spinal cord houses many ascending and descending sensory and motor tracts. Lesions in the spinal cord can cause a.o. (partial) paralysis of the muscles below lesion level, like muscles of the legs and arms, loss of sensation, neuropathic pain, incontinence, loss of sexual function, abnormal blood pressure regulation, disturbed heart rate control or impaired sweat regulation.[10] These lesions also often result in spasticity (involuntary activation) of affected muscles 10. The incidence of traumatic SCI varies from 2.3 to 83.0 per million.[11] In the Netherlands, the incidence of a traumatic SCI is about 170 individuals per year.[12] Almost 60% of lesions are incomplete lesions.[12] Early after the injury, recovery is possible, especially for individuals with incomplete lesions, however, between 9 and 18 month, recovery plateaus.[13] About 50% of ASIA B (sensory but not motor function is preserved[14]), and 75% of ASIA C (motor function is preserved in more than half of key muscles[14]) will become ambulatory.[15] During rehabilitation, recovery of walking ability has a high priority for patients with incomplete spinal cord injury.[2]

A history towards the concept of robot assisted gait therapy

In a quest to understand the neurological organization of gait, studies revealed that animal and human walking is not only controlled by the brain.[16] A large role of the neurological control of walking is reserved for the spinal cord. The spinal cord has so-called Central Pattern Generators (CPGs) which are able to generate rhythmic neural activity without input from the brain. This rhythmic activity is employed in many species for locomotion. These CPGs can be activated using sensory information from the legs without input from the brain. There are several reviews on the topic of the neurological organization of gait available in the literature.[16,17] A striking research finding on the CPG has been that cats with a fully transected spinal cord are capable of supported hind-limb stepping on a treadmill.[18] After a few weeks of therapy on a treadmill, these cats became fully weight bearing and could walk at various speeds with a near normal kinematical pattern. Since humans also possess CPGs, such findings provided the basis for the concept of walking therapy on a treadmill in humans with neurological injury. During the proposed treadmill therapy, body weight was supported by a weight bearing harness in which patients were suspended above the treadmill. It was suggested that such a therapy might tap into this CPG subsystem and contribute to enable walking in highly impaired patients[19] and this therapy seemed to be task-specific and to provide progressive practice. Gradually,

this therapy called Body Weight Supported Treadmill Training (BWSTT), was further developed and tested in experimental studies, the results of which indicated that patients who were treated with BWSTT improved more than expected compared to (historical) controls who had received conventional overground rehabilitation.[20-22] In the nineties, in more and more rehabilitation hospitals BWSTT became standard therapy in the rehabilitation after neurological injuries, especially in the United States (the NeuroRecovery Network). Typically, in rehabilitation practice, the therapy works as follows: a patient, supported by a weight bearing harness, is suspended above a treadmill while therapists assist the legs in the kinematics of walking. In some cases, a third therapist is also involved for e.g. stabilizing the torso of patients. Because of the apparent repetitive character of this type of therapy, it is suited for automation using robotics.[23,24] Therefore, at the start of this millennium, cleverly engineered, robot assisted walking devices became commercially available for rehabilitation centers. The first commercially available 'driven gait orthosis' device was the Lokomat.[23,24] The Lokomat consists of a treadmill, a body weight support system and two robotic othoses in which the legs of a patient can be strapped, to allow guidance of the leg while walking on the treadmill (Figure 1).

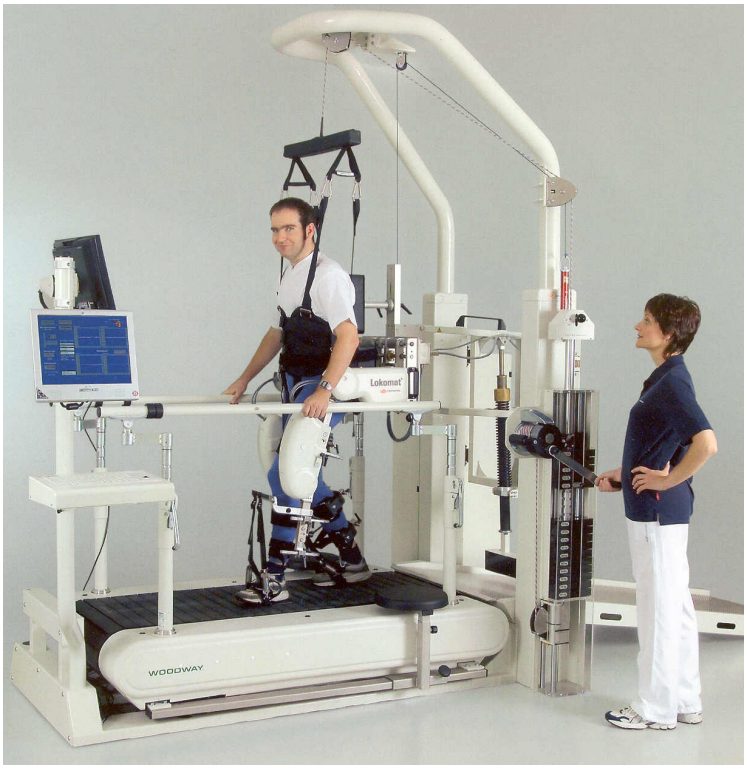

Figure 1: The Lokomat device

Possible benefits of the Lokomat

Recovery is a complex process involving both spontaneous improvements and learning dependent improvements.[25] Besides the 'spontaneous neurological recovery' present in both CVA and SCI[13,26] neurorehabilitation therapies can enhance neural recovery and help patient to learn strategies to deal with existing impairments.[26,27] Currently several recommendations are made with regard to effective therapy.[25] Therapy should start soon after neurological injury and be high-intensive, repetitive and task-specific.[25] All these ingredients are present during Lokomat therapy to improve walking ability.[28,29] Additional advantages of the Lokomat seemed to be that:

- Physical strain on trainers/clinicians is relieved
- Only a single therapist is involved
- Longer and more intensive training sessions are possible

Moreover, improving or maintaining physical fitness is another important objective of rehabilitation. Participation in aerobic training and muscle strengthening activities seems to results in higher levels of physical fitness and reduces the risk for premature chronic health conditions and mortality.[30,31] As patients may train longer at higher intensities in the Lokomat than during conventional therapies Lokomat training may have some advantages over conventional therapy as a potential aerobic exercise mode.[32]

Need for investigation

A few studies had been published showing encouraging results in pilot RCTs for both stroke and SCI by the start of this research program.[29,33-35] However, no large randomized studies were available in March 2008 and the Lokomat had been further developed in the mean time. These developments were mainly in terms of improvements in the controllers of both the bodyweight support and the algorithms of the controllers of the guidance of the legs.[36] Together, it was, therefore, deemed necessary to further study the effects of the device in terms of effectiveness in improving walking ability.

Furthermore, clinical observations had already shown that patients fatigued even after a short bout of therapy in the device, and literature suggested that treadmill walking may be used for aerobic training.[37,38] Therefore, it was anticipated that neurological patients' fitness may be improved by automated therapy. Decreased cardiorespiratory fitness might lead to a further decrease in activity resulting in a vicious circle.[39] Robot assisted therapy might be a useful tool to break this circle

by improving cardiorespiratory fitness in neurological patients. Therefore, gaining insight into the potential to improve neurological patients' fitness by automated therapy was considered important.

Aim of the thesis

The goal of this thesis was to evaluate the use of the Lokomat in rehabilitation after stroke and spinal cord injury. For this purpose several objectives were defined. The first important goal of the thesis was to evaluate Lokomat therapy in the rehabilitation of stroke patients and persons with incomplete SCI by investigating the effectiveness of an intervention with the Lokomat on recovery of walking ability. The second objective was to evaluate walking in the Lokomat in terms of muscle activity and in terms of the potential for improvements of cardiorespiratory fitness in these patients.

Outline of the thesis

Essentially, this thesis deals with two different patient groups. **Chapters 2 to 5** are related to stroke patients and **chapters 6 and 7** are related to spinal cord injured persons. This thesis starts by an evaluation of muscle activity of stroke patients during Lokomat walking compared to overground walking and of a group of able-bodied subjects during overground walking (**chapter 2**). **Chapter 3** reports whether exercise intensity during Lokomat therapy is potentially adequate to elicit a cardiorespiratory training effect in patients after stroke. Furthermore, in **chapter 3** the question of how assistance during walking in the Lokomat affects this exercise intensity is addressed. Subsequently, **chapter 4** contains the evaluation of the effectiveness of the Lokomat in improving walking ability in non-ambulatory stroke subjects involved in inpatient rehabilitation, and in **chapter 5** we examined associations between balance and strength of these stroke patients. **Chapter 6** shows whether robot-assisted gait training induces sufficiently high intensity of exercise for patients with incomplete spinal cord injury to induce improvements in cardiorespiratory fitness. Furthermore, it describes whether patients improved their cardiorespiratory fitness during an intervention of a 24 session of walking in the Lokomat (**chapter 6**). In **chapter 7**, it is investigated whether patients with lesions of the spinal cord improve in ambulatory function, balance and mobility during an intervention with the Lokomat. Finally, in the discussion (**chapter 8**) of this thesis the main findings are summarized and a selection of methodological considerations in relation to the study design, selection of study populations and outcome measures are discussed, along with clinical implications and recommendations for future research.

REFERENCES

1. Tefertiller, C., Pharo, B., Evans, N., Winchester, P., Efficacy of rehabilitation robotics for walking training in neurological disorders: A review. The Journal of Rehabilitation Research and Development, 2011. 48(4): p. 387.
2. Ditunno, P., Patrick, M., Stineman, M., Ditunno, J., Who wants to walk? Preferences for recovery after SCI: a longitudinal and cross-sectional study. Spinal Cord, 2008. 46(7): p. 500-506.
3. van de Port, I.G., Kwakkel, G., Schepers, V.P., Lindeman, E., Predicting mobility outcome one year after stroke: a prospective cohort study. J Rehabil Med, 2006. 38(4): p. 218-23.
4. Macko, R.F., Smith, G.V., Dobrovolny, C.L., Sorkin, J.D., Goldberg, A.P., Silver, K.H., Treadmill training improves fitness reserve in chronic stroke patients. Arch Phys Med Rehabil, 2001. 82(7): p. 879-84.
5. Peppen R.P.S., v., Kwakkel G., Harmeling-vander Wel B.., Kollen B.J., Hobbelen J.S.M., Buurke J.H. et al., KNGF Clinical Practice Guideline for physical therapy in patients with stroke. Review of the evidence. [Translation 2008]. Nederlands Tijdschrift voor Fysiotherapie, 2004. 2004(114;5 (Suppl)).
6. Langhorne, P., Bernhardt, J., Kwakkel, G., Stroke rehabilitation. The Lancet, 2011. 377(9778): p. 1693-1702.
7. Vaartjes, I., Dis, I.v., Visseren, F.L.J., Bots, M.L. Hart- en vaatziekten in Nederland bij vrouwen en mannen. Hart- en vaatziekten in Nederland 2011. Cijfers over leefstijl- en risicofactoren, ziekte en sterfte., ed. Vaartjes, I., et al. Vol. 2011. 2011, Den Haag: Nederlandse Hartstichting.
8. Veerbeek, J.M., Kwakkel, G., van Wegen, E.E.H., Ket, J.C.F., Heymans, M.W., Early Prediction of Outcome of Activities of Daily Living After Stroke A Systematic Review. Stroke, 2011. 42(5): p. 1482-1488.
9. Bourbonnais, D., Noven, S.V., Weakness in patients with hemiparesis. The American journal of occupational therapy, 1989. 43(5): p. 313-319.
10. Van Asbeck, F.W. Handboek dwarslaesierevalidatie. Vol. 2007. 2007: Bohn Stafleu Van Loghum.
11. Hagen, E.M., Rekand, T., Gilhus, N.E., Groning, M., Traumatic spinal cord injuries--incidence, mechanisms and course. Tidsskr Nor Laegeforen, 2012. 132(7): p. 831-7.
12. Van Asbeck, F., Post, M., Pangalila, R., An epidemiological description of spinal cord injuries in The Netherlands in 1994. Spinal Cord, 2000. 38(7): p. 420-424.
13. Fawcett, J.W., Curt, A., Steeves, J.D., Coleman, W.P., Tuszynski, M.H., Lammertse, D., Bartlett, P.F., Blight, A.R., Dietz, V., Ditunno, J., Dobkin, B.H., Havton, L.A., Ellaway, P.H., Fehlings, M.G., Privat, A., Grossman, R., Guest, J.D., Kleitman, N., Nakamura, M., Gaviria, M., Short, D., Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord, 2007. 45(3): p. 190-205.
14. Maynard Jr, F.M., Bracken, M.B., Creasey, G., Ditunno Jr, J.F., Donovan, W.H., Ducker, T.B., Garber, S.L., Marino, R.J., Stover, S.L., Tator, C.H., International standards for neurological and functional classification of spinal cord injury. American Spinal Injury Association. Spinal Cord, 1997. 35(5): p. 266.
15. Mehrholz, J., Kugler, J., Pohl, M., Locomotor training for walking after spinal cord injury.

Cochrane Database Syst Rev, 2008(2): p. CD006676.
16. Nielsen, J.B., How we walk: central control of muscle activity during human walking. The Neuroscientist, 2003. 9(3): p. 195-204.
17. Duysens, J., Clarac, F., Cruse, H., Load-regulating mechanisms in gait and posture: comparative aspects. Physiological Reviews, 2000. 80(1): p. 83-133.
18. Barbeau, H., Rossignol, S., Recovery of locomotion after chronic spinalization in the adult cat. Brain Res, 1987. 412(1): p. 84-95.
19. Barbeau, H., Blunt, R. A novel interactive locomotor approach using body weight support to retrain gait in spastic paretic subjects. Plasticity of Motoneuronal Connections ed. Wernig, A. 1991:461-474, Amsterdam, the Netherlands: Elsevier Science Publishers.
20. Wernig, A., Muller, S., Nanassy, A., Cagol, E., Laufband therapy based on 'rules of spinal locomotio' is effective in spinal cord injured persons. European Journal of Neuroscience, 1995 7: p. 823-829.
21. Wernig, A., Nanassy, A., Muller, S., Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. Spinal Cord, 1998. 36(11): p. 744-9.
22. Visintin, M., Barbeau, H., Korner-Bitensky, N., Mayo, N.E., A new approach to retrain gait in stroke patients through body weight support and treadmill stimulation. Stroke, 1998. 29(6): p. 1122-1128.
23. Colombo, G., Joerg, M., Schreier, R., Dietz, V., Treadmill training of paraplegic patients using a robotic orthosis. Journal of rehabilitation research and development, 2000. 37(6): p. 693-700.
24. Colombo, G., Wirz, M., Dietz, V., Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord, 2001. 39(5): p. 252-255.
25. Beek, P.J., Roerdink, M., Evolving insights into motor learning and their implications for neurorehabilitation, in Textbook of Neural Repair and Rehabilitation, Selzer, C., Cohen, Kwakkel, Miller, Editor. 2012 (In Press), Cambridge University Press.
26. Kwakkel, G., Kollen, B.J., Wagenaar, R.C., Understanding the pattern of functional recovery after stroke facts and theories. Restorative Neurology and Neuroscience, 2004. 22: p. 281-299.
27. Warraich, Z., Kleim, J.A., Neural plasticity: the biological substrate for neurorehabilitation. PM&R, 2010. 2(12): p. S208-S219.
28. Dobkin, B.H., Duncan, P.W., Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair, 2012. 26(4): p. 308-17.
29. Hornby, G.T., Campbell, D.D., Zemon, D.H., Kahn, J.H., Clinical and Quantitative Evaluation of Robotic-Assisted Treadmill Walking to Retrain Ambulation After Spinal Cord Injury. Topics in Spinal Cord Injury Rehabilitation, Fall/2005. 11(2): p. 1-17.
30. Galea, M.P., Spinal cord injury and physical activity: preservation of the body. Spinal Cord, 2012. 50(5): p. 344-51.
31. Gordon, N.F., Gulanick, M., Costa, F., Fletcher, G., Franklin, B.A., Roth, E.J., Shephard, T., Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing;

the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. Stroke, 2004. 35(5): p. 1230-40.
32. Hidler, J., Hamm, L.F., Lichy, A., Groah, S., Automating activity-based interventions: the role of robotics. Journal of rehabilitation research and development, 2008. 45(2): p. 337.
33. Mayr, A., Kofler, M., Quirbach, E., Matzak, H., Frohlich, K., Saltuari, L., Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair, 2007. 21(4): p. 307-14.
34. Husemann, B., Muller, F., Krewer, C., Heller, S., Koenig, E., Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 2007. 38(2): p. 349-54.
35. Wirz, M., Zemon, D.H., Rupp, R., Scheel, A., Colombo, G., Dietz, V., Hornby, T.G., Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil, 2005. 86(4): p. 672-80.
36. Riener, R., Lunenburger, L., Jezernik, S., Anderschitz, M., Colombo, G., Dietz, V., Patient-cooperative strategies for robot-aided treadmill training: first experimental results. Neural Systems and Rehabilitation Engineering, IEEE Transactions on, 2005. 13(3): p. 380-394.
37. Macko, R.F., Ivey, F.M., Forrester, L.W., Hanley, D., Sorkin, J.D., Katzel, L.I., Silver, K.H., Goldberg, A.P., Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. Stroke, 2005. 36(10): p. 2206-11.
38. Hicks, A.L., Treadmill training after spinal cord injury: It's not just about the walking. The Journal of Rehabilitation Research and Development, 2008. 45(2): p. 241-248.
39. Michael, K.M., Allen, J.K., Macko, R.F., Reduced ambulatory activity after stroke: the role of balance, gait, and cardiovascular fitness. Arch Phys Med Rehabil, 2005. 86(8): p. 1552-6.

Chapter 2

Robot-assisted walking versus overground walking in stroke patients: an evaluation of muscle activity

Pieter Coenen, Guido van Werven, Michiel P. M. van Nunen, Jaap H. Van Dieën, Karin H. L. Gerrits, Thomas W. J. Janssen

ABSTRACT

Objective: There is increasing evidence that robot-assisted treadmill training might be useful for gait rehabilitation after stroke. The aim of this study was to evaluate the muscle activity of stroke patients during robot-assisted walking and overground walking, and of a group of able-bodied subjects during overground walking.

Design: Case-control observational study.

Subjects: Ten stroke subjects and 10 able-bodied control subjects.

Methods: Electromyography measurements of 7 lower-limb muscles were made in 3 trials: robotic walking in which stroke subjects walked in a robot-assisted gait orthosis; overground walking for the same group of stroke subjects; and overground walking for control subjects. Trials were compared with respect to electromyography amplitude of selected leg muscles.

Results: Higher muscle activity during overground walking compared to robotic walking was found in several muscles during several phases of the gait cycle. During the stance phase, activity of the gluteus medius and gastrocnemius muscles was significantly lower during robot-assisted walking compared to overground walking and a significant interaction effect (trial x leg) was found in the tibialis anterior muscle. During swing phase, activity of the semitendinosus and tibialis anterior muscles were significantly lower during robot-assisted walking compared to overground walking.

Conclusion: Robot-assisted treadmill training may elicit lower muscle activity and changes in the muscle activation patterns during walking in some muscles.

INTRODUCTION

As a result of stroke, patients often show a decrease in walking speed, stride length and cycle duration as well as an asymmetrical walking pattern,[1,2] which reduces their ability to perform functional activities in daily living.[3] Since improvement in walking ability is a major requirement for independence in daily functioning, improvement in gait function is an important goal during the rehabilitation of patients following stroke.[4]

Robot-assisted walking devices have been used for a number of years during rehabilitation of stroke survivors for regaining and improving walking ability. The advantages of robot-assisted training, compared with manually assisted treadmill training, are suggested to be a longer training duration, reproducible gait kinematic patterns of the leg movements, hands-free operation by a single therapist, and reduction of the physical load imposed upon the therapist.[5-7] However, to date, there is still no consensus regarding the evidence on the possible benefits of robot-assisted treadmill training. While some studies report similar or even better training effects when comparing robot-assisted treadmill training with body-weight supported treadmill training[8,9] or other conventional therapies,[10,11] others report the opposite, with less efficacy for robot-assisted therapy[12,13] compared with conventional physical therapy. Nevertheless, a systematic review, published in 2007, suggests that stroke patients who receive electromechanical-assisted gait training in combination with physical therapy are more likely to achieve independent walking than patients receiving gait training without these devices.[14]

One of the possible disadvantages of robot-assisted gait training may be the guidance of the device, potentially reducing the effort of the patient during training at high passive guidance.[15] Another important disadvantage of robot-assisted training is the limited degrees of freedom of a robotic device restricting the walking pattern during robot-assisted walking (e.g. with the device used in the current study, one can only move in the sagittal plane in which pelvis motion is restricted). These restrictions may lead to deviations from a normal walking pattern, which can result in abnormal torque patterns,[16] leading to altered muscle activity when using such a device compared with overground walking.[17] For example, in able-bodied subjects a higher muscle activity of quadriceps muscles in the swing phase due to the restricted pelvis and a decrease in activity of the ankle flexors and extensors throughout the entire gait cycle as a result of the passive guidance has been reported.[17] Because these differences attenuated when subjects were specifically instructed to maximize their effort, it seems that the passive guidance during robot assistance should be kept as low as possible.[15] However, the above-mentioned findings are based only on studies on healthy subjects, while the actual training is meant for patients; it seems relevant to investigate whether these results can be generalized to a group of stroke

patients walking in the device. Therefore, the present study investigated muscle activity during robot-assisted treadmill walking in stroke patients. This muscle activity was compared with muscle activity during overground walking by the same stroke patients and by a group of able-bodied subjects.

METHODS

Subjects

After signing an informed consent, a group of 10 chronic stroke patients (6 men and 4 women, mean age 55 years (standard deviation (SD)[11]) with a left (n = 2) or right (n = 8) hemiparesis participated in the current study. The study was approved by the ethics committee of the VU University, Amsterdam. The hemiparesis was caused by an ischemic stroke in 5 subjects and by a hemorrhagic stroke in the other 5. The mean time since stroke was 65 (SD 47) weeks. Because the study aimed to compare robot-assisted walking with overground walking, subjects with a functional ambulation category (FAC) score of 5 were selected, indicating that they were able to walk independently on flat surfaces, stairs and slopes without assistance. The patients received conventional physical therapy training prior to the study; however, subjects had no experience of walking in a robotic device. A second group, the control group, comprised of 10 able-bodied subjects (5 men and 5 women, mean age 47 years (SD 12)) without any gait pathologies.

Study design

The group of patients after stroke participated in two measurement trials. During the robot-assisted walking trial (RW), subjects first performed a warm-up and underwent a familiarization protocol consisting of 10 min of robot-assisted walking with maximal body-weight support (BWS) and guidance force (GF). The warm-up phase was followed by a measurement period in which subjects walked in the robot-assisted walking device at a constant walking velocity of 2.2 km/hour (which was a common speed at which inpatients normally walked during therapy), with minimal support in terms of GF and BWS equal for both legs. These minimal values were determined individually for each subject by gradually reducing both GF and BWS until self-reported maximal effort was reached. During the measurement, 60 s of muscle activity data were collected. After a 10-min break to prevent possible effects of fatigue, the RW trial was followed by an overground walking trial (OW) in which subjects walked without assistance at a self-selected normal walking speed, during which data were collected for 60 s. The control group performed a walking trial (CW) at a velocity matched to the RW trial (2.2 km/hour), during which data were collected for 60 s. The CW walking trial was performed using a regular treadmill (Forcelink,

Culemborg, The Netherlands) in order to control the walking velocity.

Measurements

In this study, robot-assisted walking was performed using the Lokomat gait orthosis (Hocoma AG, Volketswil, Switzerland). This device consists of a motorized treadmill, a BWS system and two lightweight robotic actuators attached to the subjects' legs to support the leg movements during gait, allowing GF, BWS and walking speed to be controlled. The orthoses of the Lokomat were adjusted to the subjects' legs to ensure that the subject's knee and hip joints were aligned with those of the Lokomat. Foot straps were used to prevent unwanted plantar flexion.

A 16-channel electromyography (EMG) recording system with surface electrodes (Porti, Twente Medical Systems International, Oldenzaal, The Netherlands) was used for measuring muscle activity of the following muscles: medial gastrocnemius, tibialis anterior, semitendinosus, rectus femoris, adductor longus, gluteus maximus and gluteus medius. These muscles represent the muscle groups covering the main functions of the lower limbs during gait. We measured EMG in both legs in the patient group and on the right leg in the control group. Heel strikes were determined by a foot-switch (Force Sensitive Resistor, MA-153, Motion Lab Systems, Los Angeles, USA) in all conditions. All OW trials of patients were captured on video (SIMI Reality Motion Systems GmbH, Unterschleissheim, Gemany).

Data analysis and statistics

EMG signals were sampled at 1 kHz, and high-pass filtered using a 4th-order Butterworth filter with a 20-Hz cut-off frequency to remove low-frequency artifacts. Data were subsequently rectified and low-pass filtered using a 4th-order Butterworth filter with a 5-Hz cut-off frequency. In all trials, 10 gait cycles were extracted from the collected EMG data and time-normalized to gait cycle duration. Subsequently, for each muscle, EMG patterns were computed, averaging the 10 individual gait cycles to a single gait cycle of the muscle activity for each subject per trial. Detailed analysis of the muscle activity patterns was performed by dividing the EMG signal into 7 phases of the gait cycle with percentages of duration of the gait cycle according to Perry (Table 1).[18] The first phase starts with the initial contact during heel strike, as the end of the gait cycle was the subsequent initial contact of the same foot. Since it is assumed that during CW and RW a normal kinematic walking pattern in the sagittal plane is represented, these percentages were adopted to divide the time-normalized gait cycles into the different phases. A symmetric gait pattern in able-bodied subjects in terms of kinematics has already been shown in the eighties by Hannah et al.[19] A more recent review has shown that when measuring muscle activity of the lower limbs in healthy subjects reducing the amount of data by measuring just one leg

is reasonable.[20] However, since patients with hemiplegia after stroke by definition have an asymmetric kinematic walking pattern, these percentages could not be used during OW. Therefore, the time-normalized EMG signal was divided into 7 phases by means of video gait analysis (SIMI Reality Motion Systems GmbH, Unterschleissheim, Gemany). Furthermore, we broke the gait cycle up into stance and swing phase (Table 1). The level of asymmetry of the stroke patients was assessed by calculating the stance time ratio (the stance time of the paretic limb divided by that of the normal limb). A ratio of one is assumed to reflect perfect symmetry, while a ratio deviating from one reflects gait asymmetry.

Table 1. Percentages of the 7 phases of the gait cycle

Phase in gait cycle	Percentage of gait cycle
Stance phase	
Initial loading	0–10
Mid-stance	10–30
Terminal-stance	30–50
Pre-swing	50–60
Swing phase	
Initial-swing	60–73
Mid-swing	73–87
Terminal-swing	87–100

Analyses of variance (ANOVA) were performed to investigate possible differences in muscle activity of the paretic and non-paretic muscles between OW, RW and CW during all phases. In case of a significant effect of trial, Bonferroni post-hoc tests were performed. For both stance and swing phase for all 7 muscles, repeated measures analyses of variance (with mixed factorial design) were performed to investigate the muscle activity of the paretic leg and the non-paretic leg muscles during RW compared to OW. All statistical analyses were performed using SPSS (version 17.0.1). For all tests, the level of significance was set at $p< 0.05$.

RESULTS

During RW, subjects walked with a mean BWS of 45% (SD 22%) of their own weight, while the mean GF on both legs was 45% (SD 16). During OW, stroke patients walked at a mean speed of 2.8 (SD 0.5) km/h, while during RW the walking speed was set at 2.2 km/h. Furthermore, during OW subjects had a stance time ratio of 0.90 (SD 0.20), tending to deviate from 1.

Detailed analysis of muscle activity during the 7 phases of the gait cycle showed higher muscle activities in the paretic semitendinosus, gluteus medius, gastrocnemius and tibialis anterior muscle and in the non-paretic rectus femoris, semitendinosus, gluteus medius and tibialis anterior muscle during phases of OW compared to RW (Figures 1 & 2). Lower muscle activities were only found in the paretic semitendinosus in the terminal stance phase of OW compared to RW. Furthermore, differences in phases of RW and CW were found in the paretic semitendinosus and the non-paretic semitendinosus and adductor longus and gluteus medius.

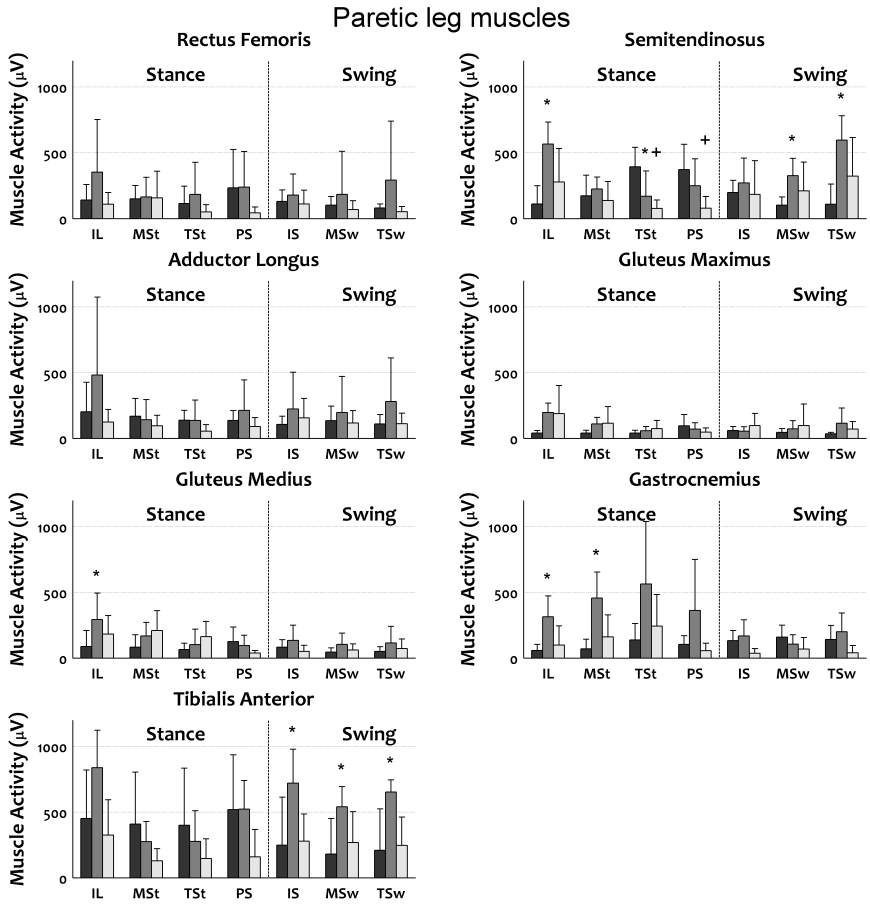

Figure 1. Mean muscle activity during robot-assisted walking (dark bars) and overground walking of the paretic muscles (grey bars) and the control group (light bars) during all 7 phases of the gait cycle. Bars represent the mean values averaged over subjects, while the standard deviations are represented by error bars. *Significant difference between the overground walking and robot-assisted walking. +Significant difference between the control group and robot-assisted walking. IL: initial loading; MSt: Mid-Stance; TSt: terminal stance; PS: pre-swing; IS: initial swing; MSw: mid-swing; TSw: terminal-swing

In the stance phase, average activity of the gluteus medius and gastrocnemius muscles was significantly lower during RW than during OW. Furthermore, for the tibialis anterior muscle an interaction between type of walking and leg was found during the stance phase; while activity in the paretic tibialis during RW was lower than during OW, the activity in the non-paretic tibialis anterior was higher during RW compared to OW (Figure 3). For the swing phase, significantly lower muscle activity was found for the semitendinosus and tibialis anterior muscles (Figure 4) compared to OW.

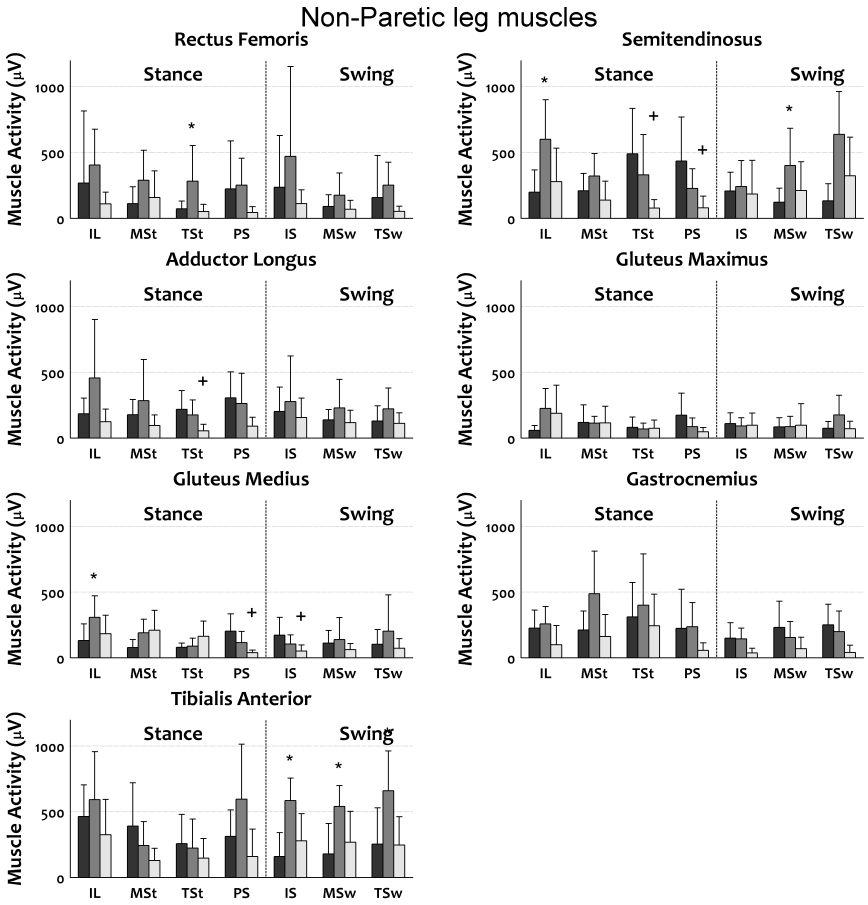

Figure 2. Mean muscle activity during robot-assisted walking (dark bars) and overground walking of the non-paretic muscles (grey bars) and the control group (light bars) during all 7 phases of the gait cycle. Bars represent the mean values averaged over subjects, while the standard deviations are represented by error bars. *Significant difference between the overground walking and robot-assisted walking. +Significant difference between the control group and robot-assisted walking. Il: initial loading; MSt: Mid-Stance; TST: terminal stance; PS: pre-swing; IS: initial swing; MSw: mid-swing; TSw: terminal-swing

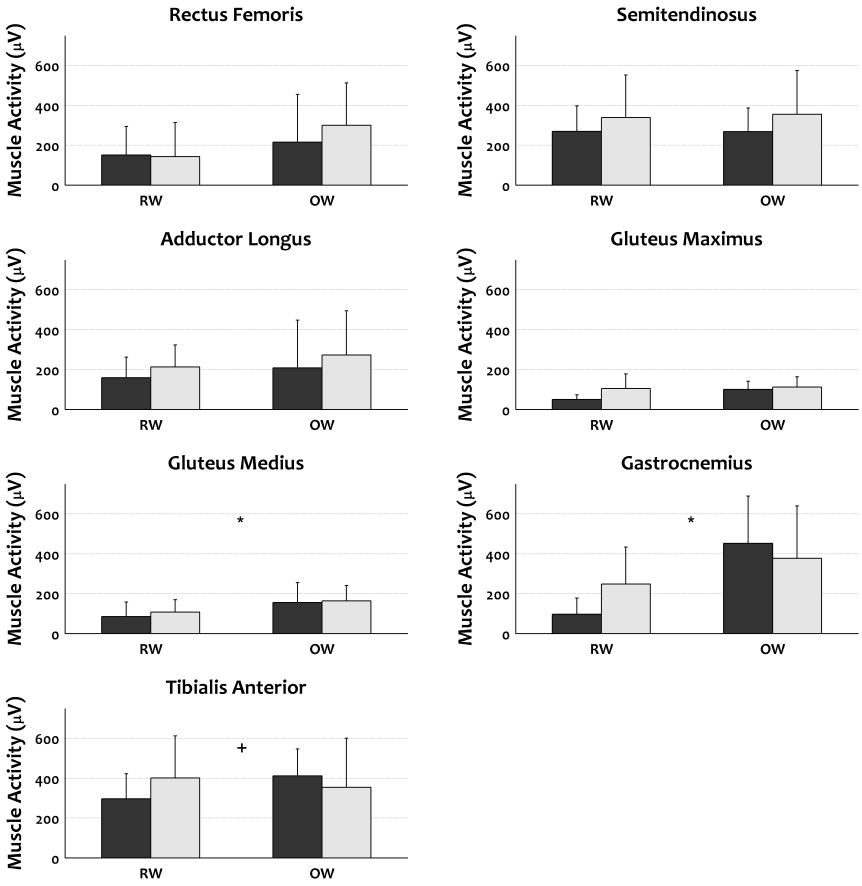

Figure 3: Mean muscle activity during stance of the muscles of the paretic (black bars) and non-paretic (grey bars) during robot-assisted walking (RW) and overground walking (OW). +Significant interaction. *Main effect for type of walking

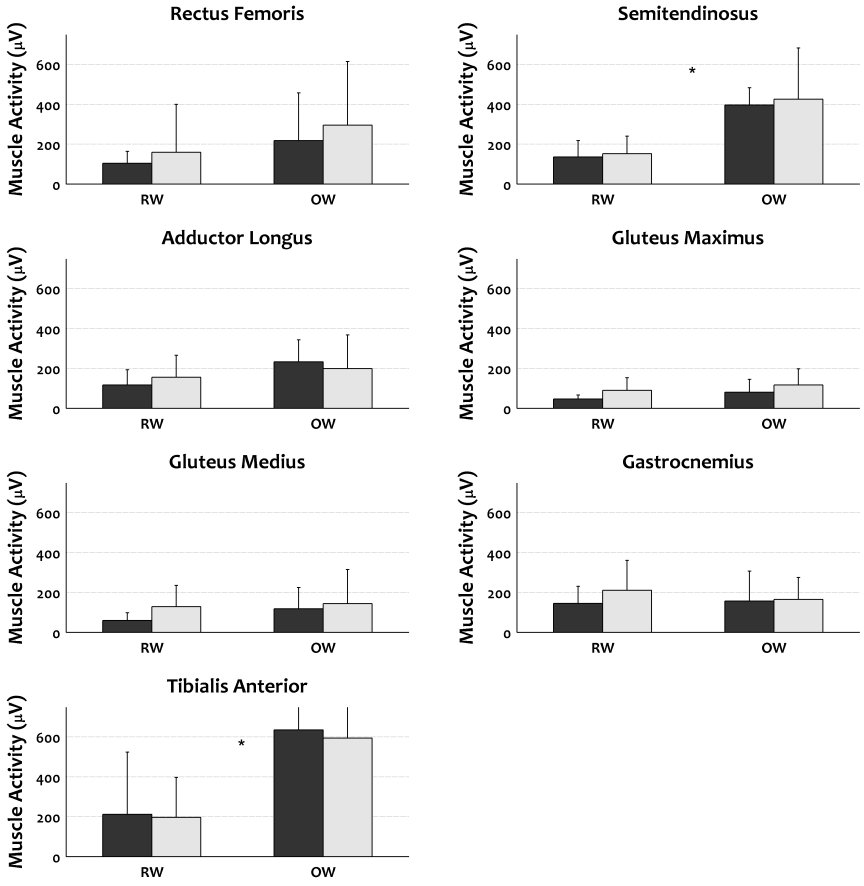

Figure 4: Mean muscle activity during swing of the muscles of the paretic (black bars) and non-paretic (grey bars) during robot-assisted walking (RW) and overground walking (OW). +Significant interaction. *Main effect for type of walking

DISCUSSION

The aim of the present study was to investigate leg muscle activation during robot-assisted treadmill walking in stroke patients compared with that in overground walking by the same stroke patients and by able-bodied subjects. For stroke patients, lower muscle activities were found in different muscles during several phases of RW compared to OW (Figures 1 & 2). Higher muscle activity during RW was only found in one phase of the gait cycle in the semitendinosus muscle. Furthermore, we found a significantly lower amplitude in gluteus medius and gastrocnemius muscles during stance in RW compared to OW (Figure 3), and a lower activity of the semintendinosus and tibialis anterior muscles during swing phase in RW compared to OW (Figure 4).

Additionally, the analysis revealed an interaction effect for the tibialis anterior during the stance phase indicating a difference in effect of type of walking for the non-paretic and paretic leg (Figure 3). The lower muscle activity during RW compared with OW suggests a lower effort during RW than during OW in these muscles, probably due to support provided by the robotic device and possibly by the restrictions of the device. The significantly lower EMG amplitudes of the gastrocnemius muscle and the gluteus medius during stance phase of walking in the Lokomat may be caused by the body weight support. Moreover, the lower activity of the gluteus medius during stance is possibly an indication that less stabilization of the hip joint is required during stance phase of RW. The interaction effect of the tibialis anterior is difficult to explain. Based on Figures 1 & 2 the interaction effect for the tibialis anterior may be explained by more activity early during stance in the paretic leg during OW, possibly through prolonged higher activity during swing phase (Figure 1). During swing phase, lower activity of the tibialis anterior can be explained by the foot straps fixing the ankle joint during the swing. The lower activity of the semitendinosus during swing of RW compared to OW may be due to the assistance of the orthoses during walking in the Lokomat. Moreover, the atypical pattern of the semitendinosus muscle activity was already demonstrated by Hidler.[17]

Comparison with previous findings

The lower muscle activity during robot-assisted treadmill walking compared with overground walking is in line with earlier findings of Israel et al.,[15] who showed that a robotic gait orthosis stabilizes the body, reducing muscle activity in quadriceps, hamstrings, tibialis anterior and calf muscles in spinal cord injured subjects. The pathological gait in stroke patients is characterized by an increased co-activation, especially around the hip, knee and ankle joints.[2] Despite the aim of the present study to reduce support during RW to a minimum, GF and BWS were reduced to only half of the full support in some subjects. This support may allow the patient to reduce the muscle activation and maybe the co-activation during RW compared with OW. This relatively high level of support needed by the patient in this study may be caused by the lack of experience in robot-assisted walking of the subjects. Furthermore, it should be noted that, in the present study, similar GFs were chosen for both legs. However, a feature of the robotic device is to apply different GFs on the two legs. The present finding can therefore be extrapolated only to training sessions in which the GF between the two legs is kept constant.

A previous study showed that muscle activity during walking in the Lokomat with 100% GF led to change in the naturally occurring muscle activation pattern in healthy subjects.[17] In the present study we can confirm this for some muscles. We found significantly lower activity in the non-paretic adductor longus, the gluteus medius and

the semitendinosus, in some phases during CW compared to RW, and a significantly lower activity the paretic semitendinosus during CW compared to RW (Figures 1 & 2). However, because EMG amplitudes are dependent on individual factors (such as skin conduction), our results should be interpreted cautiously. Nevertheless, the lack of significant differences in all phases may suggest that there is no systematic difference between EMG amplitudes between healthy and patient groups. The results suggest that walking in the Lokomat changes the naturally occurring muscle activation patterns during walking in some muscles.

Partial body weight supported treadmill training for stroke subjects has been demonstrated to result in a more symmetric walking pattern.[21] Practicing a more symmetrical gait pattern may be important to regain more symmetric gait, which is an important outcome measure in several studies on hemiparetic subjects (e.g. [22,23]). Although the restoration of gait symmetry does not seem to result in restoration in functional walking ability,[24,25] gait symmetry is positively related to local stability of walking,[26] and gait pattern variability[27] Nevertheless, allowing compensation during practice may also result in improvement in functional ability without normalized task execution, suggesting that symmetric walking should not be encouraged.The present findings do not confirm more symmetric muscle activity patterns during walking on a treadmill (during RW) compared to OW in stroke patients. This might be due to the severity of the impairments in the sample of patients participating in this experiment. The stroke subjects who participated in the current study showed a tendency to an asymmetric walking pattern, but were relatively moderately impaired compared to patients who are non-ambulatory early after stroke. It may be reasonable to expect that patients with more impaired walking ability, probably have more asymmetry during overground walking[28] which may be 'corrected' by the assistance of the Lokomat, possibly resulting in more symmetrical muscle activity. This may explain why we did not find more symmetric muscle activity in this study.

The present results represent outcomes of a robotic device consisting of robotic-driven exoskeleton actuators, which is just one approach to robotic walking. In the so-called end-effector approach of robotic walking devices,[29,30] the subjects' legs are not aligned to an exoskeleton, but only the feet are supported by moveable plates that passively move the feet in the swing and stance phase. In this approach legs are not restricted to the exoskeleton gait trajectory, possibly leading to other training effects compared with the ones during robot-assisted walking using an exoskeleton approach. In terms of muscle activity these end-effector devices have been shown to lead to muscle activity patterns comparable to those observed during overground walking in healthy subjects.[31] In addition, a randomized controlled trial, published in 2007, showed that robotic-assisted walking using an end-effector approach results in a significant improvement in gait abilities.[32] The results of the present study cannot necessarily be generalized to all types of robotic devices.

Methodological considerations

There are some characteristics of the present study that may have influenced the outcome of the study. The self-selected walking speed during OW was 0.6 km/h higher than the walking speed in RW, despite the fact that the RW speed was carefully chosen. However, a study on able-bodied subjects showed no differences in muscle activity patterns during robot-assisted walking with walking speeds ranging from 1.5 to 2.7 km/hour.[17] Another study found a proportional increase in muscle activity with an increase in walking speed in able-bodied subjects.[32] However, these differences in muscle activity pattern between different walking speeds mainly affect the amplitude of EMG. Based on this, a reduction in the differences in walking speed between the different trials in our study could have decreased the overall difference in muscle activity between the trials.

No randomization of the trials (i.e. RW and OW) was done in the current study; RW was always followed by OW. It can be argued that muscle activity patterns may therefore be biased. For example, patients might have been fatigued during the RW, which may have influenced the muscle activity patterns during the OW. Although it cannot be excluded that the differences in walking speeds between the RW and the OW trials may have led to biases in the present results, the possible effects of fatigue or learning during the trials, which may have biased the results, appear to be small, since the time of exposure to both trials was relatively short and the time of recovery between trials relatively long (10 min).

In conclusion, the results of the present study showed that leg muscle activity of chronic stroke patients is lower in robot-assisted walking than in overground walking. Despite the relatively low effort during robot-assisted treadmill training, the training may have other advantages that might make it suitable for rehabilitation of locomotor skills after stroke; for example, the duration of training can be relatively long. These results may be relevant when explaining possible training effects of the current therapy and when developing training strategies. However, no conclusions concerning long-term effects of robot-assisted walking therapy can be drawn from the present study. Whether these results hold for subjects with more severe hemiplegic gait (i.e. lower FAC scores) and for training situations with other settings of body weight support and guidance is unknown. Future studies can therefore be directed to answering these questions.

REFERENCES

1. Giuliani, C.A., Gait in rehabilitation. 1990, New York: Churchill Livingstone.
2. Olney, S.J., Richards, C., Hemiparetic gait following stroke. Gait Posture, 1996. 4: p. 136–148.
3. Kim, C.M., Eng, J.J., The relationship of lower-extremity muscle torque to locomotor performance in people with stroke. Phys Ther 2003. 83: p. 49–57.
4. Van de Port, I.G., Kwakkel, G., Schepers, V.P., Lindeman, E., Predicting mobility outcome one year after stroke: a prospective cohort study. J Rehabil Med, 2006. 38(4): p. 218-23.
5. Colombo, G., Joerg, M., Schreier, R., Dietz, V., Treadmill training of paraplegic patients using a robotic orthosis. Journal of rehabilitation research and development, 2000. 37(6): p. 693-700.
6. Colombo, G., Wirz, M., Dietz, V., Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord, 2001. 39(5): p. 252-255.
7. Hornby, T.G., Zemon, D.H., Campbell, D., Robotic-assisted, body-weight-supported treadmill training in individuals following motor incomplete spinal cord injury. Phys Ther, 2005. 85(1): p. 52-66.
8. Werner, C., Von Frankenberg, S., Treig, T., Konrad, M., Hesse, S., Treadmill training with partial body weight support and an electromechanical gait trainer for restoration of gait in subacute stroke patients: a randomized crossover study. Stroke, 2002. 33(12): p. 2895-901.
9. Hesse, S., Werner, C., Uhlenbrock, D., Frankenberg, S., Bardeleben, A., Brandl-Hesse, B., An electromechanical gait trainer for restoration of gait in hemiparetic stroke patients: preliminary results. Neurorehabil Neural Repair, 2001. 15(1): p. 39-50.
10. Mayr, A., Kofler, M., Quirbach, E., Matzak, H., Frohlich, K., Saltuari, L., Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair, 2007. 21(4): p. 307-14.
11. Husemann, B., Muller, F., Krewer, C., Heller, S., Koenig, E., Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 2007. 38(2): p. 349-54.
12. Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D.D., Kahn, J.H., Hornby, T.G., Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair, 2009. 23(1): p. 5-13.
13. Hornby, T.G., Campbell, D.D., Kahn, J.H., Demott, T., Moore, J.L., Roth, H.R., Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke, 2008. 39(6): p. 1786-92.
14. Mehrholz, J., Werner, C., Kugler, J., Pohl, M., Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev, 2007(4).
15. Israel, J.F., Campbell, D.D., Kahn, J.H., Hornby, T.G., Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther, 2006. 86(11): p. 1466-78.
16. Neckel, N.D., Blonien, N., Nichols, D., Hidler, J., Abnormal joint torque patterns exhibited by chronic stroke subjects while walking with a prescribed physiological gait pattern. J Neuroeng Rehabil, 2008. 5: p. 19.
17. Hidler, J.M., Wall, A.E., Alterations in muscle activation patterns during robotic-assisted walking. Clin Biomech (Bristol, Avon), 2005. 20(2): p. 184-93.

18. Perry, J., Gait Analysis. 1992, Thorofare, NJ: Slack Inc.
19. Hannah, R.E., Morrison, J.B., Chapman, A.E., Kinematic symmetry of the lower limbs. Arch Phys Med Rehabil, 1984. 65(4): p. 155-8.
20. Sadeghi, H., Allard, P., Prince, F., Labelle, H., Symmetry and limb dominance in able-bodied gait: a review. Gait Posture, 2000. 12(1): p. 34-45.
21. Hesse, S., Konrad, M., Uhlenbrock, D., Treadmill walking with partial body weight support versus floor walking in hemiparetic subjects. Arch Phys Med Rehabil, 1999. 80(4): p. 421.
22. Hesse, S., Helm, B., Krajnik, J., Gregoric, M., Mauritz, K.H., Treadmill training with partial body weight support: influence of body weight release on the gait of hemiparetic patients. Neurorehabil Neural Repair, 1997. 11(1): p. 15-20.
23. Winstein, C.J., Gardner, E.R., McNeal, D.R., Barto, P.S., Nicholson, D.E., Standing balance training: effect on balance and locomotion in hemiparetic adults. Arch Phys Med Rehabil, 1989. 70(10): p. 755-62.
24. De Haart, M., Geurts, A.C., Huidekoper, S.C., Fasotti, L., van Limbeek, J., Recovery of standing balance in postacute stroke patients: a rehabilitation cohort study. Arch Phys Med Rehabil, 2004. 85(6): p. 886-895.
25. Den Otter, A.R., Geurts, A.C., Mulder, T., Duysens, J., Gait recovery is not associated with changes in the temporal patterning of muscle activity during treadmill walking in patients with post-stroke hemiparesis. Clin Neurophysiol, 2006. 117(1): p. 4-15.
26. Dingwell, J.B., Cusumano, J.P., Sternad, D., Cavanagh, P.R., Slower speeds in patients with diabetic neuropathy lead to improved local dynamic stability of continuous overground walking. J Biomech, 2000. 33(10): p. 1269-77.
27. Van Emmerik, R.E.A., Hamill, J., McDermott, W.J., Variability and coordinative function in human gait. Quest, 2005. 57(1): p. 102-123.
28. Roerdink, M., Geurts, A.C., de Haart, M., Beek, P.J., On the relative contribution of the paretic leg to the control of posture after stroke. Neurorehabil Neural Repair, 2009. 23(3): p. 267-74.
29. Schmidt, H., Werner, C., Bernhardt, R., Hesse, S., Krüger, J., Gait rehabilitation machines based on programmable footplates. J Neuroeng Rehabil, 2007. 4(1): p. 2.
30. Hesse, S., Werner, C., Connecting research to the needs of patients and clinicians. Brain Res Bull, 2009. 78(1): p. 26-34.
31. Hussein, S., Schmidt, H., Volkmar, M., Werner, C., Helmich, I., Piorko, F., Kruger, J., Hesse, S. Muscle coordination in healthy subjects during floor walking and stair climbing in robot assisted gait training. in Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE. 2008. IEEE.
32. Pohl, M., Werner, C., Holzgraefe, M., Kroczek, G., Mehrholz, J., Wingendorf, I., Hoolig, G., Koch, R., Hesse, S., Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil, 2007. 21(1): p. 17-27.

Chapter 3

Exercise intensity of robot-assisted walking versus overground walking in non-ambulatory stroke patients

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Thomas W. J. Janssen

ABSTRACT

It has been suggested that aerobic training should be considered in stroke rehabilitation programs to counteract detrimental health effects and decrease cardiovascular risk caused by inactivity. Robot-assisted treadmill exercise (using a Lokomat device) has the potential to increase the duration of walking therapy relative to conventional overground therapy. We investigated whether exercise intensity during Lokomat therapy is adequate to elicit a training effect and how assistance during walking in the Lokomat affects this exercise intensity.

Ten stroke patients (54±9 yrs) walked in both the Lokomat and in a hallway. Furthermore, 10 nondisabled subjects (43±14 yrs) walked in the Lokomat at various settings and on a treadmill at various speeds. During walking, oxygen consumption and heart rate were monitored.

Results showed that for patients, exercise intensity did not reach recommended levels (30% HRR) for aerobic training during Lokomat walking. Furthermore, exercise intensity during walking in the Lokomat device (9.3±1.6 ml/min/kg) was lower than during overground walking (10.4±1.3 ml/min/kg). Different settings of the Lokomat only had small effects on exercise intensity in nondisabled subjects.

INTRODUCTION

A large portion of patients with stroke initially has no walking ability and cannot walk independently because of hemiparesis and compromised balance. Moreover, a subgroup is not able to walk independently, even after a few months into the rehabilitation process. The inability of walking independently or being active has been suggested to lead to further deconditioning and is related to balance.[1] Secondary impairments, such as muscle atrophy and reduced aerobic capacity, have been reported and suggested to contribute to further functional declines in gait.[2] To counteract detrimental health effects and to decrease cardiovascular risk due to inactivity, it has been suggested that aerobic training should be considered in stroke rehabilitation programs.[3-6] Although there are probably differences among approaches in different countries and different rehabilitation centers, both Kuys et al.[7] and MacKay-Lyons et al.[4] showed that contemporary stroke rehabilitation programs in Canada and Australia did not elicit adequate exercise intensity for aerobic training.

In recent years, a device for robot-assisted gait therapy (Lokomat, Hocoma AG; Volketswil, Switzerland) was developed to automate body-weight supported treadmill training for severely disabled patients. The Lokomat consists of a treadmill with a body-weight support system and two robotic orthoses that guide the individual's legs, allowing patients to walk for longer duration and making more repetitions possible during therapy.[5] Several studies have investigated the effectiveness of the Lokomat in restoring walking ability.[8-10] However, there is a lack of studies related to exercise intensity of Lokomat therapy and the potential for facilitating aerobic training in severely affected patients with stroke.

Walking in the Lokomat has been shown to increase oxygen consumption ($\dot{V}O_2$) above resting levels in patients and nondisabled subjects without experience walking in the Lokomat, indicating that walking in the Lokomat is not passive.[11] It is, however, still largely unknown whether exercise intensity of walking in the Lokomat during the rehabilitation process of stroke patients is within levels of intensity for aerobic training as recommended by the American College of Sports Medicine.[12] Furthermore, there is little knowledge about how assistance during walking in the Lokomat influences exercise intensity of walking. E.g., in severely affected patients, walking speed in the Lokomat can be much higher than during overground walking. From the literature it is known that walking at a higher speed requires more energy,[13,14] and therefore one could expect exercise intensity to increase during Lokomat walking compared to overground walking. However, body-weight support has been shown to decrease $\dot{V}O_2$ during treadmill walking.[15] Also, the Lokomat assists the legs during walking, potentially decreasing exercise intensity.[16] Finally, during walking in the Lokomat, the position of the pelvis is held constant relative to the treadmill, thereby decreasing the horizontal propulsion force and at the same time decrease energy cost during

walking.[14] Combined, these factors complicate predictions of effects of assistance on exercise intensity during Lokomat walking.

To improve our understanding of the exercise intensity of Lokomat walking during therapy, our primary objective was to investigate the exercise intensity during Lokomat therapy and compare this to exercise intensity recommendations of the American College of Sports Medicine. The second objective was to compare exercise intensity of walking in the Lokomat with normal overground gait in patients with stroke. Since patients can walk for longer duration in the Lokomat and the device provides assistance during walking, we hypothesized that patients with stroke walking in the Lokomat walked at lower exercise intensity than during normal gait. The third objective was to evaluate how different settings of the Lokomat affect exercise intensity during walking on the device. We hypothesized that with increased assistance, exercise intensity of walking in the Lokomat decreases.

METHODS

General design

Participants came to the laboratory to perform two experimental sessions: walking in the Lokomat and walking in a hallway. Nondisabled subjects performed one experimental session consisting of Lokomat walking and unassisted walking on a treadmill. We collected cardiorespiratory parameters during each walking session.

Lokomat device

The design and control of the Lokomat has been reported previously.[7] In this study, the LokomatPro device (Hocoma, Switzerland) was used with the LEVI bodyweight support system. In all trials for both patients and able bodied subjects, the LEVI bodyweight support system was activated. Three settings were manipulated during this study: speed, amount of body-weight support (BWS) and Guidance Force (GF), which is the amount of assistance of the robotic orthoses.

Subjects

Ten hemiplegic stroke patients (6 male and 4 female; 54 ± 9 yrs) and ten nondisabled subjects (6 male and 4 female; 43 ± 14 yrs) participated in the study. Patients had a first-ever stroke and had no unstable hypertension, no unstable cardiovascular problems, no severe skeletal problems or severe cognitive and/or communicative problems preventing the ability to follow verbal instructions. All procedures were approved by the local ethics committee and all subjects gave written informed consent before participation. Table 1 presents patient characteristics such

as age, sex, lesion side, and time poststroke. Functional limitations are described using the Functional Ambulation Category (FAC) and Berg Balance Scale (BBS). The FAC score is a 6-point measure for walking ability,[17,18] FAC scores below 3 indicate dependent walking ability, while 3 indicates supervision needed. The BBS, developed to qualitatively asses balance, consists of 14 test items scored on a 5-point ordinal scale.[19]

All patients had already received therapy in the Lokomat for at least 7 times before the first measurements were performed. Eight patients had been training on the Lokomat as part of their inpatient treatment to improve walking ability. Two patients were asked to participate in the study after their discharge from the rehabilitation centre. Patients were, therefore, familiar with walking in the Lokomat and settings were fine-tuned to the patients' capabilities. In this study, nondisabled subjects had at least two practice sessions of 30 minutes in the Lokomat to get familiarized to walking in the device with various combinations of speed, BWS and GF.

Table 1: Characteristics of patients

Patient	Age (yrs)	Time post stroke (wks)	Side of lesion	Gender	FAC	BBS
1	53	10	L	M	2	28
2	47	52	R	M	3	35
3	43	79	R	F	3	22
4	71	11	R	F	2	14
5	53	25	L	M	3	16
6	62	18	R	M	2	17
7	64	12	R	M	2	24
8	47	16	R	M	3	44
9	49	12	R	F	3	35
10	50	12	R	F	2	24
Mean ± SD	**54 ± 9**	**25 ± 23**			**2.6 ± 0.5**	**26 ± 9**

General procedures

We measured $\dot{V}O_2$ and heart rate (HR) as indices of cardiorespiratory responses. During the Lokomat and treadmill trials, we continuously monitored $\dot{V}O_2$ with an Oxycon Alpha (Jaeger Germany). During the overground trials of patients, an Oxycon Mobile lightweight portable spirometer (Jaeger, Germany) was used to measure $\dot{V}O_2$. This portable system was attached to the chest with a comfortable vest (1.1 kg). We continuously monitored HR with an HR monitor (Polar RS400, Polar Electro; Kempele, Finland)

Patients with Stroke

During the experiments, we strapped the paretic arm using an arm sling as a precaution to prevent shoulder pain. We measured baseline resting $\dot{V}O_2$ in the seated position for 3 min. After preparation for Lokomat therapy, patients walked in the Lokomat while we monitored $\dot{V}O_2$ and HR. Lokomat settings were the same as those used for the patients' regular therapy settings and were individually optimized in such a way that they walked at a comfortable walking speed (CWS) with GF of the device kept at a minimum level and appropriate BWS without knee buckling during the stance phase. We used settings from previous therapy sessions as reference settings for the trials in the Lokomat and adjusted settings if necessary.

Before patients with stroke performed overground walking, we measured baseline resting $\dot{V}O2$ during sitting at the start of the experiment for 3 minutes. Subsequently, patients were instructed to walk at a comfortable speed along a 20-meter walkway. A physical therapist walked closely behind the patients either for supervision or for assistance in maintaining balance. After 20 meters, patients turned and walked the walkway in the other direction. Patients walked for 6 minutes continuously before sitting down or until they needed to sit down because walking became too strenuous. All subjects walked with their usual aids for overground walking: a quad cane and an ankle foot orthosis.

We averaged recorded $\dot{V}O_2$ and HR data over 60-s intervals. We determined $\dot{V}O_2$ during rest ($\dot{V}O_{2rest}$), the highest $\dot{V}O_2$ during the session ($\dot{V}O_{2peak}$), and the average $\dot{V}O_2$ over the interval between the third minute and the third last minute of walking ($\dot{V}O_{2avg}$) during both Lokomat walking and during overground walking and expressed them in both absolute values and in metabolic equivalents (METs). We computed METs using the formula $\dot{V}O_2/\dot{V}O_{2rest}$. Variables associated with HR were the lowest HR during rest (HR_{rest}), HR at $\dot{V}O_{2peak}$ (HR_{peak}), and average HR (HR_{avg}).

We estimated exercise intensity using the Karvonen method, with the heart rate reserve (HRR) being the difference between HR_{rest} and the age-predicted maximal HR, estimated using the formula HR_{max}=220-age. For the patient using beta-blocking medication (n=1), the formula was adjusted by HR_{max}-beta=0.85 x (220-age).[4,20] We estimated exercise intensity by expressing the HR relative to HRR (%HRR).[12] ACSM guidelines for sedentary/extremely deconditioned nondisabled adults recommend training at a %HRR of 30%-45%.[12] Both HR_{avg} and HR_{peak} were expressed as %HRR and compared to these recommendations.

Nondisabled Control Subjects

Since patients with stroke are not capable of walking in the Lokomat at any combination of settings possible, we studied the effects of settings of the Lokomat in nondisabled subjects only. Resting $\dot{V}O_2$ was measured during three minutes of

seated rest. Nondisabled subjects walked in the Lokomat at eight combinations of settings, similar to those used during rehabilitation of stroke patients. We set speed at either 1.7 or 2.2 km/h, GF at either 50 or 20 percent, and BWS at either 50 or 25 percent of body weight, resulting in eight (2 × 2 × 2) different conditions. After the Lokomat trials, nondisabled subjects rested a few minutes. The nondisabled subjects subsequently walked on a treadmill performing 4 walking trials at different treadmill speeds (0.7 km/h, 1.1 km/h, 1.7 km/h and 2.2 km/h). All trials were performed for three minutes. We further analyzed minimal HR during rest (HR_{rest}) and average $\dot{V}O_2$ and HR during the last minute of all the Lokomat and treadmill only trials. The formulas used to estimate %HRR were also used to determine exercise intensity in nondisabled subjects.

Statistical analysis

We tested data for normality using Shapiro-Wilk tests. We performed paired t-tests to investigate whether exercise intensity (as measured with $\dot{V}O_2$ and %HRR) of Lokomat walking was different from normal overground gait in patients. To study the effects of several combinations of settings of the Lokomat on $\dot{V}O_2$ or %HRR, a three-way repeated measures ANOVA was performed, with within factors BWS (25% or 50%), GF (20% or 50%) and speed (1.7 km/h or 2.2 km/h) on the Lokomat trials only. Furthermore, 2 ANOVAs tested whether there was a difference in $\dot{V}O_2$ or %HRR between trials performed at the same speed with or without the assistance of the Lokomat. In these two ANOVAs, four Lokomat trials were compared to the treadmill trial at the same speed, for 1.7 km/h and 2.2 km/h respectively. Post hoc analyses were performed using paired t-tests with Bonferroni correction when appropriate.

To evaluate whether patients and nondisabled subjects responded in a similar manner to assistance of the Lokomat, we performed a two-way (mixed design) ANOVA on $\dot{V}O_2$ and %HRR data with a between-subjects factor 'group' (patients and nondisabled subjects) and a within-subject factor 'mode of walking' (Lokomat or no Lokomat). During the overground trial of patients, the average speed was 0.7 ± 0.2 km/h. For comparison, the trials for nondisabled subjects included in this analysis were the trials with walking speed of 0.7 km/h for normal walking and the Lokomat trial with theoretically the least assistance of the device (settings 2.2 km/h, BWS 25% and GF 20%), since these trials were the most comparable to the trials performed by patients. Homogeneity of variances was tested using Levene's test for homogeneity of variances. Finally, we performed a t-test to investigate whether $\dot{V}O_2$ during Lokomat walking was similar for the subjects groups. Probability values of less than .05 were considered significant. All analyses were performed using PASW v18.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Exercise intensity of Lokomat walking for stroke subjects

Table 2 shows a summary of the characteristics of the trials performed by patients are shown. One of the ten patients showed an individual exercise intensity which was above 30%HRR. For patients, exercise intensity expressed in METs was within the range defined as light physical activity intensity for the lowest fitness level group according to ACSM guidelines.

All variables and differences were normally distributed. In patients, the peak $\dot{V}O_2$ during overground walking (10.4 ± 1.3 ml/min/kg) was significantly higher than during Lokomat walking (9.3 ± 1.6 ml/min/kg), $t(9) = 2.83$, $p < .02$, mean difference 1.1 ml/min/kg, 95% CI[0.2 1.9]. Correspondingly, HR_{peak} during overground walking (104 ± 14 beats per minute [bpm]) was significantly higher than during Lokomat walking (92 ± 12 bpm), $t(9) = 2.59$, $p < .03$, mean difference HR 12.4 pbm, 95% CI [1.5 23.2].

Table 2 : Performance parameters during oveground and Lokomat trials

	Overground	Lokomat
$Velocity_{peak}$ (km/h)	0.7 (0.2)	2.1 (0.1)
BWS_{peak} (%)	-	33 (9)
GF_{peak} (%)	-	29 (6)
Endurance (sec)	5.1 (0.8)	26 (5)
$\dot{V}O_{2peak}$ (ml/min/kg)	10.4 (1.3)	9.3 (1.6)
$\dot{V}O_{2avg}$(ml/min/kg)	9.9 (1.4)	7.8 (1.5)
HR_{peak} (bpm)	104 (14)	92 (12)
HR_{avg} (bpm)	104 (13)	89 (13)
METS	2.8 (0.3)	2.1 (0.3)
$\%HRR_{peak}$	38 (13)	25 (7)
$\%HRR_{avg}$	38 (12)	22 (7)

Effects of settings of the Lokomat on exercise intensity

For nondisabled subjects, Table 3 shows $\dot{V}O_2$ and HR during all trials with corresponding settings of the device. Average $\dot{V}O_2$ and HR values during different Lokomat conditions are very similar for all eight different settings (L1-L8) and for the normal gait trials (N1-N4).

Table 3: Settings with corresponding $\dot{V}O_2$ and HR during Lokomat walking (L1-L8) and treadmill only walking (N1-N4)

	BWS	Speed	GF	$\dot{V}O_2$ (ml/min/kg)	HR (bpm)
Rest				3.7 ± 0.4	60 ± 8
L1	50%	1.7 km/h	50%	7.9 ± 2.6	76 ± 10
L2	50%	1.7 km/h	20%	8.4 ± 2.3	79 ± 9
L3	50%	2.2 km/h	50%	7.9 ± 1.7	78 ± 10
L4	50%	2.2 km/h	20%	8.4 ± 2.2	79 ± 13
L5	25%	1.7 km/h	50%	7.8 ± 1.4	77 ± 9
L6	25%	1.7 km/h	20%	8.9 ± 2.3	79 ± 9
L7	25%	2.2 km/h	50%	8.0 ± 1.4	76 ± 13
L8	25%	2.2 km/h	20%	8.2 ± 1.8	77 ± 12
N1		0.7 km/h		7.0 ± 1.0	72 ± 9
N2		1.1 km/h		7.1 ± 0.8	74 ± 10
N3		1.7 km/h		7.9 ± 0.7	76 ± 11
N4		2.2 km/h		8.6 ± 0.9	77 ± 12

The three-way (2 × 2 × 2) repeated measures ANOVA revealed a significant higher effect for lower GF on $\dot{V}O_2$ ($F(1,9)=6.84$, $p<.03$ $\eta 2=0.43$) and HR ($F(1,9)=8.57$, $p<.02$, $\eta 2=0.49$). When GF was set at 20%, mean $\dot{V}O_2$ is 0.57 ml/min/kg higher, (95% CI [0.08 1.06]) and mean HR was 1.9 bpm higher (95% CI [0.4 3.4]) than during GF of 50%. Furthermore, there was a borderline significant interaction effect of BWS and speed in HR data, $F(1,9)=5.20$, $p<.049$, $\eta^2=0.37$, indicating that when BWS was 50%, walking at 2.2 km/h elicited a higher HR compared to 1.7 km/h, whereas when the BWS was 25%, walking at 2.2 km/h elicited a lower HR compared to 1.7km/h. However, the differences between means were small (e.g. maximal difference was 2.3 b/min), therefore the interaction effect had a small effect size.

The ANOVA's comparing trials performed at similar speeds (4 Lokomat trials and one treadmill only trial at 1.7 km/h or 2.2 km/h, respectively) comparable results. There were no significant differences in $\dot{V}O_2$ ($F(2.6,23.8)=1.58$, $p>.05$, $\eta^2=0.15$) and HR ($F(2.4,21.7)=2.83$, $p>.05$, $\eta 2=0.24$) between trials with walking speed of 1.7 km/h. $\dot{V}O_2$ at this speed was 8.2 ± 1.7 ml/min/kg and HR was 77 ± 9 bpm. Similarly, at 2.2 km/h there were also no significant differences in $\dot{V}O_2$, $F(1.9, 16.7)=1.25$, $p>.05$, $\eta^2=0.12$, and HR, $F(4, 36)=0.92$, $p>.05$ $\eta 2=0.09$. $\dot{V}O_2$ at this speed was 8.2 ± 1.4 ml/min/kg and HR was 78 ± 11 bpm. This indicates that, although subjects were assisted by the Lokomat, exercise intensity was not different from normal, unassisted walking when walking at the same speeds.

Exercise intensity during walking in patients vs. nondisabled subjects

As a group, patients had a significantly higher $\dot{V}O_2$ (9.8 ml/min/kg, 95% CI[9.0 10.6]) than nondisabled subjects (7.6 ml/min/kg, 95% CI[6.8 8.5]), $F(1,18)=15.67$, $p<0.001$, $\eta^2=0.47$ (Figure 1) across different modes of walking. There was no significant difference between $\dot{V}O_2$ during Lokomat walking and normal gait for the whole group, $F(1, 18)=0.36$, $p>.05$, $\eta^2=0.002$. There was, however, a significant interaction between 'mode of walking' and 'group', $F(1, 18)=11.21$, $p<.005$, $\eta^2=0.38$. Results of the analysis for %HRR were similar, i.e. patients had significantly higher %HRR (31.4 %HRR, 95% CI[27 36]) than nondisabled subjects (12.3 %HRR, 95% CI[8 16]), $F(1,18)=45.40$, $p<.001$, $\eta^2=0.72$ (Figure 1). There was no significant main effect for 'mode of walking', $F(1, 18)=2.80$, $p>.05$, $\eta^2=0.13$, but there was a significant interaction between 'mode of walking' and 'group' $F(1, 18)=12.00$, $p<.005$, $\eta^2=0.4$. These statistical results confirm what Figure 1 indicates: patients responded differently than nondisabled subjects with different types of walking, i.e., while patients showed a lower $\dot{V}O_2$ and %HRR during Lokomat walking, the nondisabled subjects showed higher values during Lokomat walking than during normal walking at 0.7 km/h. Subsequent analysis showed no significant difference in $\dot{V}O_2$ during Lokomat walking in patients ($\dot{V}O_2$ 9.3 ± 1.6 ml/min/kg) compared to nondisabled subjects ($\dot{V}O_2$ 8.2 ± 1.8 ml/min/kg) $t(18) = -1.36$, $p > .05$, mean difference 1.0 ml/min/kg, 95% CI [-0.6 2.6], indicating that $\dot{V}O_2$ during walking in the Lokomat were similar for patients and nondisabled subjects.

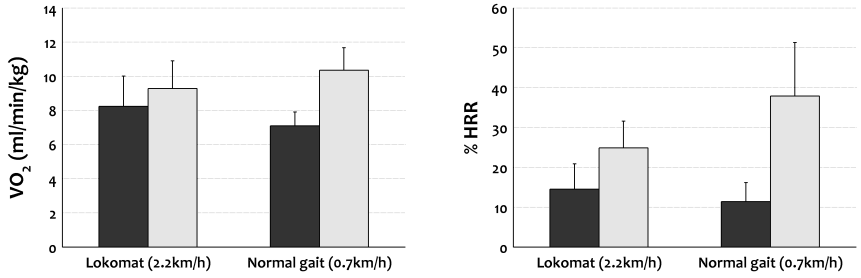

Figure 1: $\dot{V}O_2$ and HRR during Lokomat walking and normal gait for both patients (grey) and nondisabled subjects (black).

DISCUSSION

In this study, we compared exercise intensity of walking in the Lokomat with exercise intensity of normal gait in both patients with stroke and nondisabled subjects. Results indicate that the exercise intensity in patients was below levels recommended by the American College of Sports Medicine for sedentary/extremely deconditioned nondisabled adults (30%HRR),[12] i.e. the absolute minimum level. Furthermore, this

study shows that exercise intensity of walking in the Lokomat is lower than during normal gait in severely disabled stroke patients. To evaluate the effects of settings of the Lokomat, nondisabled subjects walked at various combinations of settings, and it was demonstrated that the influence of settings of the Lokomat on $\dot{V}O_2$ and HR is marginal. Finally, it was demonstrated that, when walking in the Lokomat is compared to overground walking, patients responded differently to assistance of the device than nondisabled subjects.

Exercise intensity of Lokomat walking for patients

Our study suggests that, based on the estimates of exercise intensity, the target training intensities (30%HRR) were not reached for most patients when walking in the Lokomat. Nevertheless, a recent study by Chang et al.[21] showed that after only two weeks of intervention, a group of patients with stroke training in the Lokomat had a larger improvement of $\dot{V}O_{2peak}$ as measured during an incremental exercise test than a group on control patients receiving conventional therapy. Note, however, that differences in recovery of function between groups might also be responsible for an increase similar to that observed by Chang et al.[21] This confounding factor should be taken into account during exercise tests in the (sub)acute stroke patient population. Nevertheless, the advantage of Lokomat therapy is the longer possible duration of therapy. This may explain the findings of Chang et al.[21] Furthermore, in a small randomized clinical trial, Huseman et al. reported an effect of Lokomat therapy on body tissue composition, which they suggested being due to increased aerobic metabolism.[22] More research is warranted to study the effects of Lokomat therapy on cardiorespiratory fitness.

Effects of settings of the Lokomat on exercise intensity

Therapists have a range of settings to control during Lokomat walking. We only investigated the 3 main variables treadmill speed, body-weight support and amount of assistance.[23] Krewer et al.[11] demonstrated that using a lower BWS increased $\dot{V}O_2$ when changed from 100% unloading to 30% BWS. Furthermore, they showed that neither speed nor GF had a significant effect on $\dot{V}O_2$. When compared to our study, lower levels of $\dot{V}O_2$ were found in Krewer et al.,[11] which was probably due to other settings (e.g. lower speeds, or possibly other BWS system) or the better walking ability of patients in their study. In our study, we wanted to investigate the effect on $\dot{V}O_2$ and HR of various settings used during therapy. The observed significant effects were very small, therefore, it can be concluded that the effects of changing settings within the ranges used in this study are only small and the clinical relevance is therefore questionable.

Furthermore, for nondisabled subjects, exercise intensity of gait at 1.7 km/h and

2.2 km/h was similar for all trials performed at these speeds. We expected that the assistance of the device would decrease $\dot{V}O_2$ and HR relative to unsupported normal walking based on findings in the literature.[15] The absence of such an effect may be explained by other factors that may have counterbalanced the assistance of the device, such as the requirement to follow a prescribed gait pattern. Wezenberg et al. showed that enforcing a normal step pattern increased metabolic energy cost of walking during treadmill walking.[24] It seems plausible that similar mechanisms are responsible for the results in the present study.

Exercise intensity during walking in patients vs. nondisabled subjects

We found a difference in the way patients responded to the assistance of the Lokomat device compared to nondisabled subjects. Patients showed a lower $\dot{V}O_2$ and %HRR during Lokomat walking, whereas nondisabled subjects showed higher $\dot{V}O_2$ and %HRR during Lokomat walking than during normal walking at 0.7 km/h. These results are probably mostly due to observations already described in the literature[25] that at similar speeds, hemiparetic walking is more energy demanding than nondisabled walking, with growing disparity with more affected hemiparetic gait. Figure 1 shows that the differences between exercise intensity of walking became smaller between subject groups when walking in the Lokomat was compared to normal gait. There was no significant difference between patients and nondisabled subjects during walking in the Lokomat. These findings confirm what Krewer et al.[11] concluded, that for a given walking condition, patients performed similar as nondisabled subjects. This might indicate that cardiorespiratory responses of nondisabled subjects might be more similar to cardiorespiratory responses of patients during Lokomat walking compared to responses observed during overground walking.

Limitations of the study

Limitations of this study are the differences between patients in settings during Lokomat walking and the difference in overground walking speed for patients compared to nondisabled subjects. These differences may increase variability among subjects when patients are compared to the nondisabled subject group, and thereby decrease power of the statistics. However, when the two-way (2 × 2) factor ANOVA was repeated with data from the other Lokomat trials and the 1.2 km/h treadmill trial of nondisabled subjects (not shown), the results were the same as reported. The conclusion for the differences between patients and nondisabled subjects remains unaltered.

It is possible that the exercise intensity of Lokomat walking might still be somewhat higher with more sophisticated settings (such as asymmetrical settings) over the levels recorded in our study. By using voluntary efforts, exercise intensity can

also be increased as demonstrated by Jack et al.[26,27] They showed that in incomplete patients with spinal cord injuries, $\dot{V}O_2$ can increase markedly when subjects actively push against the robotic orthoses while walking. It is unclear whether this can also be achieved by severely disabled stroke patients, however, it can be argued that the already altered muscle activity during walking in the Lokomat[28] would be further changed.

We instructed patients (and nondisabled subjects) to walk as normally as possible and follow the prescribed gait pattern. For severely affected patients, further decrease of the BWS and/or the GF will most likely not be possible because the prescribed gait pattern will not be followed properly; the precautions present in the Lokomat will intervene by stopping the device to immediate stand still when there is too much deviation from the prescribed gait pattern. Furthermore, walking with more challenging settings may not be perceived as comfortable and it remains to be seen whether patients are still capable and willing to walk for 20 minutes or longer at these more challenging settings of the Lokomat.

The conclusions of this study do not necessarily extrapolate to other robot assisted devices. However, a few studies similar to our present study have been recently performed with a similar device,[29,30] In line with the discussion above, these studies showed that only with the right settings it is possible to train patients at intensities sufficiently high for aerobic training effects.

Conclusions and recommendations

From this study it can be concluded that exercise intensity during Lokomat walking is light and below ACSM recommended values to improve aerobic fitness. Furthermore, changing settings within certain ranges prescribed and used for severely disabled patients has only a small influence on exercise intensity.

Although our results suggest that the exercise intensity with Lokomat walking is most likely insufficient to elicit an aerobic training effect, there are indications that low-intensity training (at 30%HRR) may increase peak aerobic capacity,[31] and that in stroke patients, Lokomat training might improve aerobic capacity[21] and body tissue composition.[22] These inconsistencies warrants further research to study the effects of training in the Lokomat on aerobic capacity and further investigation on how severely affected patients can exercise in the Lokomat at higher exercise intensities using other combinations of settings.

REFERENCES

1. Michael, K.M., Allen, J.K., Macko, R.F., Reduced ambulatory activity after stroke: the role of balance, gait, and cardiovascular fitness. Arch Phys Med Rehabil, 2005. 86(8): p. 1552-6.
2. Macko, R.F., Smith, G.V., Dobrovolny, C.L., Sorkin, J.D., Goldberg, A.P., Silver, K.H., Treadmill training improves fitness reserve in chronic stroke patients. Arch Phys Med Rehabil, 2001. 82(7): p. 879-84.
3. Ivey, F.M., Hafer-Macko, C.E., Macko, R.F., Exercise training for cardiometabolic adaptation after stroke. J Cardiopulm Rehabil Prev, 2008. 28(1): p. 2-11.
4. MacKay-Lyons, M.J., Makrides, L., Cardiovascular stress during a contemporary stroke rehabilitation program: Is the intensity adequate to induce a training effect? Arch Phys Med Rehabil, 2002. 83(10): p. 1378-1383.
5. Colombo, G., Wirz, M., Dietz, V., Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord, 2001. 39(5): p. 252-255.
6. Wendel-Vos, G., Schuit, A., Feskens, E., Boshuizen, H., Verschuren, W., Saris, W., Kromhout, D., Physical activity and stroke. A meta-analysis of observational data. International Journal of Epidemiology, 2004. 33(4): p. 787.
7. Kuys, S., Brauer, S., Ada, L., Routine physiotherapy does not induce a cardiorespiratory training effect post-stroke, regardless of walking ability. Physiotherapy Research International, 2006. 11(4): p. 219-227.
8. Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D.D., Kahn, J.H., Hornby, T.G., Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair, 2009. 23(1): p. 5-13.
9. Schwartz, I., Sajina, A., Neeb, M., Fisher, I., Katz-Luerer, M., Meiner, Z., Locomotor training using a robotic device in patients with subacute spinal cord injury. Spinal Cord, 2011. 49(10): p. 1062-7.
10. Mehrholz, J., Werner, C., Kugler, J., Pohl, M., Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev, 2007. 2007 oct (17 (4)).
11. Krewer, C., Muller, F., Husemann, B., Heller, S., Quintern, J., Koenig, E., The influence of different Lokomat walking conditions on the energy expenditure of hemiparetic patients and healthy subjects. Gait Posture, 2007. 26(3): p. 372-7.
12. ASCM's Guidelines for Exercise Testing and Prescription, eighth edition, Thompson, W.R., Editor 2011, Wolters Kluwer | Lippincott Williams & Wilkins.
13. Waters, R.L., Mulroy, S., The energy expenditure of normal and pathologic gait. Gait Posture, 1999. 9(3): p. 207-31.
14. Griffin, T.M., Roberts, T.J., Kram, R., Metabolic cost of generating muscular force in human walking: insights from load-carrying and speed experiments. J Appl Physiol, 2003. 95(1): p. 172-83.
15. Danielsson, A., Sunnerhagen, K.S., Oxygen consumption during treadmill walking with and without body weight support in patients with hemiparesis after stroke and in healthy subjects. Arch Phys Med Rehabil, 2000. 81(7): p. 953-7.
16. Gottschall, J.S., Kram, R., Energy cost and muscular activity required for propulsion during walking. J Appl Physiol, 2003. 94(5): p. 1766-72.
17. Holden, M.K., Gill, K.M., Magliozzi, M.R., Nathan, J., Piehl-Baker, L., Clinical gait assessment

in the neurologically impaired. Reliability and meaningfulness. Phys Ther, 1984. 64(1): p. 35-40.
18. Holden, M.K., Gill, K.M., Magliozzi, M.R., Gait assessment for neurologically impaired patients. Phys Ther, 1986. 66(10): p. 1530.
19. Blum, L., Korner-Bitensky, N., Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review. Phys Ther, 2008. 88(5): p. 559-66.
20. Pollock, A., Baer, G., Langhorne, P., Pomeroy, V., Physiotherapy treatment approaches for the recovery of postural control and lower limb function following stroke: a systematic review. Clin Rehabil, 2007. 21(5): p. 395-410.
21. Chang, W.H., Kim, M.S., Huh, J.P., Lee, P.K., Kim, Y.H., Effects of Robot-Assisted Gait Training on Cardiopulmonary Fitness in Subacute Stroke Patients: A Randomized Controlled Study. Neurorehabil Neural Repair, 2011.
22. Husemann, B., Muller, F., Krewer, C., Heller, S., Koenig, E., Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 2007. 38(2): p. 349-54.
23. Hesse, S., Werner, C., Paul, T., Bardeleben, A., Chaler, J., Influence of walking speed on lower limb muscle activity and energy consumption during treadmill walking of hemiparetic patients. Arch Phys Med Rehabil, 2001. 82(11): p. 1547-50.
24. Wezenberg, D., de Haan, A., van Bennekom, C.A., Houdijk, H., Mind your step: metabolic energy cost while walking an enforced gait pattern. Gait Posture, 2011. 33(4): p. 544-9.
25. Zamparo, P., Francescato, M.P., De Luca, G., Lovati, L., di Prampero, P.E., The energy cost of level walking in patients with hemiplegia. Scand J Med Sci Sports, 1995. 5(6): p. 348-52.
26. Jack, L.P., Purcell, M., Allan, D.B., Hunt, K.J., Comparison of peak cardiopulmonary performance parameters during robotics-assisted treadmill exercise and arm crank ergometry in incomplete spinal cord injury. Technol Health Care, 2010. 18(4-5): p. 285-96.
27. Jack, L.P., Purcell, M., Allan, D.B., Hunt, K.J., The metabolic cost of passive walking during robotics-assisted treadmill exercise. Technol Health Care, 2011. 19(1): p. 21-7.
28. Hidler, J.M., Wall, A.E., Alterations in muscle activation patterns during robotic-assisted walking. Clin Biomech (Bristol, Avon), 2005. 20(2): p. 184-93.
29. Mehrholz, J., Werner, C., Hesse, S., Pohl, M., Immediate and long-term functional impact of repetitive locomotor training as an adjunct to conventional physiotherapy for non-ambulatory patients after stroke. Disabil Rehabil, 2008. 30(11): p. 830-6.
30. David, D., Regnaux, J.P., Lejaille, M., Louis, A., Bussel, B., Lofaso, F., Oxygen consumption during machine-assisted and unassisted walking: a pilot study in hemiplegic and healthy humans. Arch Phys Med Rehabil, 2006. 87(4): p. 482-9.
31. Van Den Berg, R., De Groot, S., Swart, K.M., Van Der Woude, L.H., Physical capacity after 7 weeks of low-intensity wheelchair training. Disabil Rehabil, 2010. 32(21): p. 1717-21.

Chapter 4

Recovery of walking ability using a robotic device in stroke patients: a randomized controlled study

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ABSTRACT

Background: Robot-assisted treadmill training with the Lokomat device has been used to improve walking ability in rehabilitation after stroke for more than a decade. This study investigates the effectiveness of the Lokomat in recovering walking ability in non-ambulatory stroke subjects involved in inpatient rehabilitation.

Method: Thirty first-ever stroke patients completed 8 weeks of intervention. One group (n=16) received Lokomat therapy twice a week, combined with 3 times 30 minutes a week of conventional overground therapy. The second group (n=14) received conventional assisted overground therapy only, during a similar amount of time (3.5 hours a week). The intervention was part of the normal rehabilitation program. Primary outcome measure was walking speed. Secondary outcome measures assessed other walking- and mobility-related tests, lower-limb strength, and quality of life measures. All outcome measures were assessed before and after the intervention and at wk24 and wk36 after start of the intervention.

Results: Patients showed significant ($p<.05$) gains in walking speed, other walking- and mobility related tests and strength of the paretic knee extensors relative to baseline at all assessments. However, there were no significant differences in improvements in any of the variables between groups at any time during the study.

Conclusion: These results indicate that robot-assisted treadmill training is as effective as conventional training in recovering walking ability in non-ambulatory stroke patients.

INTRODUCTION

Recovery of walking ability is one of the main goals during rehabilitation after stroke since it is an important factor in becoming independent in activities of daily life. Outcome of therapy is, however, still unsatisfactory in many cases, manifesting itself in decreased walking speed, asymmetric gait and decreased mobility compared to the healthy population.[1,2] In practice, several types of therapy are employed to advance walking ability,[3-5] such as overground gait training with assistance of a therapist or body weight supported treadmill training (BWSTT). In a Cochrane review, BWSTT was demonstrated to be no more effective than conventional overground therapy in improving walking ability.[6] In search of more effective therapies, scientists, physicians and therapists have focused their attention on developing and using robot assisted therapy in the last decade.[7] The theoretical advantage of robot assisted therapy is that it provides the opportunity to patients to start training early after their stroke, to practice walking longer and train with a more repetitive gait pattern.[8-10]

On the basis of results of pilot studies, there was substantial enthusiasm for the clinical use of these robot assisted devices.[11] Presently, several devices, such as the Lokomat,[12] are commercially available and other new devices are in the developmental stage (e.g. LOPES[13]). The Lokomat, developed to automate BWSTT for severely disabled patients, consists of a body weight support system and two robotic orthoses that guide the individual's legs during walking on a treadmill.[6,7] When the present study was first initiated (Nov. 2008) there were only a few randomized controlled studies available in the literature on the effectiveness of the Lokomat.[11,14,15] These studies reached conflicting conclusions on whether Lokomat therapy is more effective than conventional therapy in the rehabilitation after stroke. Therefore, setting up a new randomized controlled study (RCT) was deemed necessary. Presently, more randomized controlled studies have been published on the effectiveness of the Lokomat;[16-19] Two studies found negative effects for Lokomat therapy,[11,16] two studies reported beneficial effects[14,17] and another three studies found no differences between therapy effects.[15,18,19] Besides differences in patient population (in ability at baseline and time after stroke), one possible reason for these conflicting results may be that the amount of assistance of the orthoses during walking varied across studies; three of the studies used a fully enforced gait trajectory,[11,16,18] three others allowed a decreased amount of assistance of the orthoses[14,15,19] and one study did not reveal specifics about the amount of assistance.[17] It is suggested that when using an enforced gait pattern, the effort level of patients might not be the highest because the Lokomat completely assists in the kinematic trajectory and therapy may therefore not be optimal.[16] Furthermore, only two studies performed follow-up measurements,[11,16] both of which used a fully enforced gait pattern. If only short-term effects are measured, important information about the 'end-point' of therapy

is missing. Currently, there is no study investigating both the short term intervention effect of the Lokomat using less guidance of the orthoses and the time course of further gains during a follow-up period.

The purpose of the present study, therefore, was to compare walking related improvements obtained after Lokomat therapy in combination with conventional overground therapy versus conventional overground therapy alone in stroke patients who were not able to walk independently. Secondary goals were to compare long term follow-up outcome measures and to investigate whether possible differences in recovery of walking ability between groups could be explained by changes in other outcome measures (e.g. differences in improvements in strength of the legs) and whether this would result in differences in amelioration of quality of life (QOL). We hypothesized that Lokomat therapy would elicit greater gains in walking ability, function, and mobility than conventional overground therapy aimed at recovery of walking ability with therapist assistance. Furthermore, we hypothesized that these improvements would be sustained at follow-up measurements.

METHODS

Initial sample size calculations based on an alpha of 5% and a power of 80% indicated that we needed 40 patients in each group to demonstrate a difference between groups in walking speed of 0.1 m/s seconds at wk10. Participants were recruited by screening admissions at Reade Center for Rehabilitation and Rheumatology in Amsterdam. Patients participating in the study had a first-ever supratentorial stroke. Other inclusion criteria were: hemiparesis, ≥18 years, inability to walk completely independently at start of the intervention, no unstable hypertension, no unstable cardiovascular problems, no severe skeletal problems or severe cognitive and/or communicative problems preventing the ability to follow verbal instructions. All procedures were approved by the local ethics committee and all subjects gave written informed consent before participation. Patients were randomly (block randomization) assigned to either a robot-assisted therapy group or a conventional therapy group. The 8-week intervention consisted of 3.5 hours of physical therapy a week aimed at improving walking ability. The robot-assisted therapy group received 2 hours of robot assisted treadmill training and 1.5 hours a week of conventional physical therapy aimed at recovery of walking ability (PT), whereas the conventional therapy group underwent 3.5 hours of PT. The therapy time aimed at walking was hence dose-matched across the two intervention groups. Patients received the intervention as part of normal inpatient rehabilitation therapy (consisting of e.g. physical therapy for the upper limb, occupational therapy or speech therapy individualized for each patient). We chose this design because we wanted to investigate a design that was financially and practically feasible within the restrictions of the Dutch health care

reimbursement system. After the intervention period, patients received standard, but individualized rehabilitation therapy, either for a period of inpatient rehabilitation or a period of home-based rehabilitation.

Robot-assisted treadmill training

Robot-assisted treadmill training was administered using the Lokomat. The design and control of the Lokomat has been reported previously.[12] In this study, the LokomatPro device (Hocoma, Switzerland) was used with the LEVI bodyweight support system. Three settings were manipulated during this study: speed, amount of body weight support (BWS) and the amount of assistance of the robotic orthoses (Guidance Force: GF).

The first therapy session was used to adjust the device properly to the individual patient and allow the patient to get comfortable with walking in the device. In subsequent sessions patients were instructed to actively follow the walking pattern of the device. Initial speed was normally around 1.5 km/h at which speed we decreased the BWS up to a point where the patients were still able to support the weight on the legs during the stance phase without knee buckling. Simultaneously, we decreased the GF initially by 20%. As soon as we thought the patients had sufficient experience with the device, we activated the LEVI bodyweight support system and again made sure there was adequate BWS (i.e. no knee buckling). Using this system, weight support was regulated by a computer instead of a passive spring system. In following therapy sessions, we gradually increased speed (normally up to 2.5 km/h), decreased BWS (up to 10%) and decreased GF (up to 20%) in order to challenge the patient to walk as actively as possible with as little assistance of the device as possible. We used settings the patients were still able to walk with for about 20-30 minutes without getting exhausted. The ultimate goal was to walk at high but still comfortable speed, with as little BWS and GF as possible for as many minutes possible within the therapy time.

Assisted overground therapy

Overground assisted therapy (PT) was administered following guidelines of the Dutch Guidelines for Physical Therapy in patients with stroke 20, meaning that patients recieved assistance during walking of a therapist and assistive device(s) such as a cane or quad cane, horizontal bars or an ankle foot orthosis.

Outcome measures

Outcome measures were evaluated by assessors not blinded to treatment allocation of the patients. Primary outcome measure was walking speed at the 10m timed walk test assessed at baseline (wk1), at post-intervention (wk10), and at wk24 and wk36 after start of the study. However, we only measured walking speed when patients had at least a Functional Ambulation Category (FAC) score of 2 (i.e. patient needed continuous or intermittent support of one person to help with balance and coordination). Since not all patients had this walking ability at baseline, especially during the early part of the intervention we were not able to measure walking speed in a group of patients. Walking speed was set to zero when patients had a FAC score below 2.

Secondary outcome measures were also collected at baseline, at post-intervention and at wk24 and wk36 after start of the study. Outcome measures for walking ability, function and mobility were FAC, Berg Balance Scale (BBS), Motricity index (MI), Brunnstrom-Fugl-Meyer (FM), and Rivermead Mobility Index (RMI). For patients with a FAC≥3 we also measured 'Timed Up and Go' test (TUG). Furthermore, we measured maximal voluntary isometric torque of the knee extensors (MVT_{ext}) and knee flexors (MVT_{flex}) of both the paretic leg (P) and the non-paretic leg (NP) using a custom-built system 21 to investigate whether training in the Lokomat induced differences in lower-limb muscle strength. During the torque measurements, subjects were seated with a hip angle of 100° (180° being fully extended hips) and knee angle of 60° (0°= full extension) while the lower leg was strapped tightly to a force transducer. Movements of the leg and changes in hip and knee angles during force generation were minimized by tightly strapped hip and trunk belts to ensure isometric contractions. Finally, we assessed quality of life measures with the Short Form 36 (SF-36) and the Stroke Impact Scale (version 3.0, SIS 3.0). With these outcome measures we were able to determine improvements in walking ability, function and mobility, lower-limb strength, and quality of life measures.

Statistical Analysis

Group differences between the Lokomat and the conventional therapy in patient characteristics and baseline values for all outcome variables were analyzed using independent samples t-tests for continuous, normally distributed variables and Mann-Whitney U tests for categorical variables.

Since walking speed at baseline was not normally distributed because of the 'zero' walking speed of a number of patients (see Table 1), we used Mann-Whitney U tests to analyze the differences in the primary outcome variable walking speed between groups at baseline. Subsequently, at wk10, wk24 and wk36, changes in walking speed relative to baseline values were calculated. These change scores of walking speed

were analyzed using ANCOVA with correction for baseline values.[22-24] The effect size for the differences in gains between groups was calculated using r.[25]

Secondary variables were analyzed similarly; we calculated changes in outcome measures by subtracting baseline values from the absolute values at each time point. Subsequently we performed ANCOVA with correction for baseline values on these change scores.[22-24] Baseline values for TUG test were not available for the majority of the subjects (because TUG can only be performed when patients have FAC≥3), therefore change scores relative to baseline could not be calculated. Alternatively, we analyzed the available absolute TUG scores at each measurement using Mann Whitney U test in order to investigate between group differences in TUG. A $p < .05$ was considered statistically significant. The effect size for the differences in gains between groups was calculated using r.[25]

All analyses were performed using PASW version 18.0. When parametric tests were used, means with standard deviation are reported. When non-parametric tests were used, median and interquartile range (IQR) are reported.

We were also interested in between-group differences in gains during the follow-up period. Therefore, for all variables, we calculated the change scores relative to wk10 and analyzed the differences between groups in change scores during the follow-up period using ANCOVA with correction for outcome measures at wk10.

RESULTS

Of the 37 patients enrolled in the study, 6 withdrew from the study within the intervention period because of a decline in health unrelated to the study (n=4), or refusal to further participate in the intervention due to pain (n=1) or fear (n=1). Furthermore, one patient was excluded from the study after randomization because location of the lesion had been incorrectly screened. Another 3 patients dropped out of the study before the first follow-up (wk24) because of travel limitations (n=1) or refusal to return for the measurements (n=2). One subject was not able to attend the follow-up measurement at wk24, but did return at wk36. At the last follow up (wk 36), another 6 patients were lost: one patient had a second stroke, one patient was on vacation for 2 months, two patients refused to return for the last measurement and two patients had travel limitations. By the final measurement at wk36, 6 out of 16 patients in the Lokomat group and 3 out of 14 patients in the control group had been lost to follow-up.

An interim conditional power analysis was performed based on the available data. This analysis revealed that in total 160 patients were needed to be recruited to demonstrate a significant difference in treatment effect (with alpha of 5 % and power of 80%). Since the time to recruit this number of patients was not available, we decided to stop the trial before the planned number of patients was recruited.

Table 1 shows characteristics of the patients and distribution of baseline measures of FAC scores per group. Of the 30 patients who completed the intervention period, 16 had been assigned to the Lokomat group, whereas 14 were assigned to the conventional therapy group. There were no significant differences in these characteristics between the groups at baseline.

Table 1: Patient characteristics and baseline (wk1) values for walking ability

	Lokomat (n=16)	**Conventional (n=14)**	**p-value**
Age (SD) in years	50.0 (9.6)	56.0 (8.7)	.08#
Days post stroke (SD)	61.6 (28.7)	67.1 (49.1)	.70#
Gender (M/F)	10/6	5/8	.29*
Side of stroke (R/L)	5/11	5/9	.80*
Ischemic/hemorrhagic	9/7	10/4	.40*
BMI (SD)	23.6 (3.9)	25.7 (4.0)	.16#
FAC (0/1/2/3)§	-/8/5/3	2/6/4/2	.45*

* P value represents between-group comparison obtained with Mann Whitney U test. # P value represents between-group comparison obtained with t-test. § FAC=0: patient cannot ambulate/FAC=1: continuous physical assistance in support of bodyweight and balance required/FAC=2: continuous or intermittent physical assistance in balance required/FAC=3: supervision required.

Primary outcome measure walking speed

There were no significant differences (p=.93) in walking speed at baseline between Lokomat (0.03 m/s, IQR=0.14) and the conventional therapy group (0.00 m/s, IQR=0.22). Patients had a significantly higher walking speed at all assessments relative to baseline (Table 2). However, there were no significant differences in improvements in walking speed between the intervention groups after the intervention period (wk10) or at the follow-up measures at wk24 and wk36 after start of the study (Figure 1, Table 2). Effect size ranged from 0.11 for the differences at wk10 (post-intervention) to 0.25 for the differences at wk36 indicating a small to moderate effect.

Table 2: Secondary outcome measures: function and mobility

Measure (n per group: L/C)	Lokomat	Conventional	Effect size (r)	p-value†	p-value‡
Walking speed (m/s)					
baseline (16/14)	0.03 (IQR=0.14)	0.00 (IQR=0.23)		.93*	-
Δ wk 10 (16/14)	0.20 (0.16)	0.17 (0.17)	0.11	.57#	.00
Δ wk 24 (14/12)	0.31 (0.27)	0.21 (0.21)	0.20	.34#	.00
Δ wk 36 (10/11)	0.39 (0.30)	0.26 (0.21)	0.25	.28#	.00
FAC					
baseline (16/14)	1.50 (IQR=1.0)	1.00 (IQR=1.00)		.45*	-
Δ wk 10 (16/14)	1.25 (0.58)	1.29 (0.99)	0.00	.98#	.00
Δ wk 24 (14/12)	2.00 (0.88)	2.00 (1.13)	0.02	.91#	.00
Δ wk 36 (10/11)	2.60 (0.84)	2.27 (1.42)	0.22	.34#	.00
BBS					
baseline (16/14)	16.0 (IQR=17.3)	11.5 (IQR=23.8)		.27*	-
Δ wk 10 (16/14)	14.4 (9.5)	15.0 (9.6)	0.01	.94#	.00
Δ wk 24 (14/12)	17.4 (14.7)	17.9 (10.2)	0.09	.64#	.00
Δ wk 36 (10/11)	21.7 (12.2)	20.4 (12.0)	0.12	.60#	.00
RMI					
baseline (16/14)	5.0 (IQR=2.8)	5.0 (IQR=2.3)		.40*	-
Δ wk 10 (16/14)	3.8 (2.0)	3.8 (2.0)	0.05	.78#	.04
Δ wk 24 (14/12)	5.8 (2.3)	5.6 (2.4)	0.02	.90#	.00
Δ wk 36 (10/11)	6.5 (2.2)	6.1 (2.5)	0.13	.56#	.00
FM leg					
baseline (16/14)	13.0 (IQR=7.3)	14.0 (10.3)		.69*	-
Δ wk 10 (16/14)	2.6 (1.9)	3.1 (2.0)	0.13	.44#	.03
Δ wk 24 (14/12)	2.6 (4.2)	4.0 (2.2)	0.10	.63#	.02
Δ wk 36 (10/11)	4.0 (2.8)	5.4 (4.3)	0.15	.52#	.01
TUG					
baseline (6/5)	63 (IQR=37)	70 (IQR=72)		.47*	-
wk 10 (15/10)	45 (IQR=27)	41 (IQR=38)	0.00	1.0*	-
wk 24 (14/9)	47 (IQR=37)	42 (IQR=30)	0.08	.70*	-
wk 36 (10/9)	32 (IQR=24)	37 (IQR=42)	0.20	.37*	-

L/C: Lokomat/Conventional therapy group. † P value between group differences. ‡ P value change over time. * P value represents between-group difference obtained with Mann-Whitney-U test. # P value represents between-group difference corrected for baseline values obtained with ANCOVA. Δ Indicate change in outcome measure from wk1, positive value means improvement.

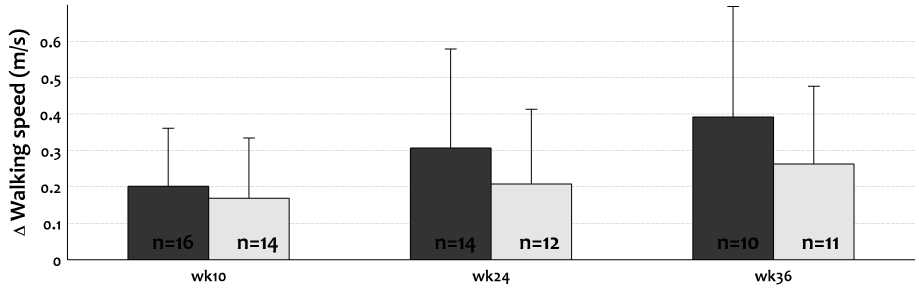

Figure 1: Average change (and SD) in walking speed relative to baseline at wk10 and at the two follow-up measurements wk24 and wk36.

Secondary variables

As shown in table 2, there were no significant differences in baseline values of FAC, BBS, RMI, FM leg and TUG between the Lokomat therapy group and the conventional therapy group. Patients significantly improved in all variables from baseline to wk10, wk24 and wk36 respectively. However, there were no significant differences in change scores for FAC, BBS, RMI, FM leg and TUG between the Lokomat therapy group and the conventional therapy group. Furthermore, there were also no significant differences between groups in gains during the follow-up period from wk10 to wk24 or from wk10 to wk36 for FAC, BBS, RMI, FM leg and TUG. Effect size ranged from 0.00 to 0.22 indicating small to moderate effects.

In table 3 the average values for the MVT measurements of both legs are shown for each group. Patients' knee extension strength of the NP leg (MVT_{extNP}), the knee flexion strength of the NP leg (MVC_{flexNP}) and the flexion strength of the paretic (P) leg (MVT_{flexP}) did not significantly change in the intervention period. The knee extension strength of the P leg significantly improved at wk10, wk24 and wk36 relative to baseline. However, there were no significant differences between the Lokomat group and the conventional overground therapy group in changes in the MVT of the knee extensors or of the knee flexors of either leg. Effect size ranged from 0.08 to 0.30 indicating small to moderate effects.

Table 3: Average MVT for knee extensors and flexors for the non-paretic as well as the paretic leg

Measure (n per group: L/C)	Lokomat	Conventional	Effect size (r)	p-value†	p-value‡
MVT_{extNP} (Nm)					
baseline (16/14)	145 (42)	133 (37)		.45°	-
Δ wk 10 (16/13)	7 (21)	0 (15)	0.22	.26#	0.17
Δ wk 24 (11/10)	10 (29)	27 (24)	0.26	.26#	0.08
Δ wk 36 (9/5)	27 (20)	38 (48)	0.16	.58#	0.35
MVT_{extP} (Nm)					
baseline (16/14)	50 (IQR=46)	21 (IQR=39)		.06*	-
Δ wk 10 (16/12)	6 (20)	15 (15)	0.19	.31#	0.01
Δ wk 24 (11/10)	14 (29)	37 (29)	0.23	.30#	0.00
Δ wk 36 (8/5)	21 (23)	42 (36)	0.19	.53#	0.00
MVT_{flexNP} (Nm)					
baseline (16/14)	52 (23)	55 (19)		.76°	-
Δ wk 10 (16/13)	4 (13)	-3 (7)	0.29	.13#	0.30
Δ wk 24 (11/10)	10 (14)	4 (16)	0.21	.36#	0.11
Δ wk 36 (9/5)	14 (18)	7 (6)	0.23	.43#	0.66
MVT_{flexP} (Nm)					
baseline (16/14)	3 (IQR=7)	3 (IQR=7)		.74*	-
Δ wk 10 (16/13)	3 (6)	0 (3)	0.30	.11#	0.05
Δ wk 24 (11/10)	0 (7)	2 (8)	0.17	.45#	0.12
Δ wk 36 (8/5)	7 (9)	6 (5)	0.08	.79#	0.07

L/C: Lokomat/Conventional therapy group. † P value between group differences. ‡ P value change over time. * P value represents between-group difference obtained with Mann-Whitney-U test. °P value represents between-group difference obtained with t-test. # P value represents between-group difference corrected for baseline values obtained with ANCOVA. Δ Indicate change in outcome measure from wk1, positive value means improvement.

Table 4 lists the outcome of general health, social functioning, mobility and activities of daily life measured by the SF-36 and the SIS 3.0. The first 3 subjects were not assessed using the questionnaires, and some subjects were not willing to fill out the questionnaires, especially at follow-up at wk24 and wk36, resulting in additional missing values at follow-up. Therefore, in table 4 the results of the assessments using questionnaires are shown for the subset of patients for wk10 only. Patients significantly ameliorated in general health, social functioning, mobility and activities of daily life over the intervention period. However, we found no significant differences between groups in changes over time. Effect size ranged from 0.04 to 0.25 indicating small to moderate effects.

Table 4: General health, social functioning, activities of daily life and mobility

Measure (n per group: L/C)	Lokomat	Conventional	Effect size (r)	p-value†	p-value‡
SF 36: General health					
baseline (12/12)	45 (IQR=23)	48 (IQR=24)		0.95*	
Δ wk 10 (12/12)	-0 (20)	8 (16)	0.25	0.25#	.04
SF 36: Social functioning					
baseline (12/12)	19 (IQR=72)	25 (IQR=72)		0.79*	
Δ wk 10 (12/12)	7 (32)	17 (36)	0.24	0.24#	.00
SIS 3.0: Activities of daily life					
baseline (12/12)*	34 (IQR=39)	38 (IQR=22)		0.91*	
Δ wk 10 (12/12)	7 (21)	12 (18)	0.16	0.45#	.00
SIS 3.0: Mobility					
baseline (12/12)	29 (IQR=34)	38 (IQR=33)		0.91*	
Δ wk 10 (12/12)	10 (22)	9 (28)	0.04	0.86#	.00

L/C: Lokomat/Conventional therapy group. † P value between group differences. ‡ P value change over time. * P value represents between-group difference obtained with Mann Whitney U test. # P value represents between-group difference corrected for baseline values obtained with ANCOVA. ΔIndicate change in outcome measure from wk1, positive value means improvement

DISCUSSION

This study reports the results of a randomized clinical study on the effectiveness of an intervention with Lokomat therapy compared to conventional assisted overground therapy on the recovery of walking ability in non-independently walking stroke subjects in the Netherlands. During the course of this study, the primary outcome measure walking speed improved concurrently with secondary variables FAC, BBS, RMI, TUG, FM-leg, quality of life measures and knee extension strength of the paretic leg. These results are in line with literature demonstrating that changes in balance control and strength are associated with changes in walking ability.[26] Furthermore, patients did not regain or improve the ability to generate knee flexion force of the paretic leg in the test position, or the strength of the non-paretic leg. However, this study also shows that substitution of Lokomat therapy in the conventional rehabilitation program did not induce larger gains in any of the outcome measures than in conventional assisted overground therapy. Therefore, we reject our hypothesis that employing Lokomat therapy elicits greater gains than conventional overground therapy.

The lack of a difference in effect of the interventions might be partially explained by the moderate difference between the two interventions. Both groups received a total of 3.5 hours a week of physical therapy focused on walking ability. For

the control group, this consisted of 7 sessions of 30 minutes a week of assisted overground therapy, whereas for the Lokomat group this consisted of 2 session of one hour duration on the Lokomat combined with 3 sessions of 30 minutes a week of assisted overground therapy. During Lokomat therapy we decreased the amount of GF (assistance by the orthoses) of the legs as much as possible thereby eliciting more variability in stepping, which has been shown to be more effective than a fixed training trajectory in stepping rats.[27] Although patients were upright relatively longer and walked faster during therapy in the Lokomat than during assisted overground therapy, the assistance of the device and the restrictions in possible movements[16] may not have provided an equally suitable learning environment as during overground therapy. Apparently, the difference between intervention therapies was not sufficient to result in differences in gains in walking related outcome measures or in strength of the legs during the intervention period. Nevertheless, it may be possible that patients can be more effectively trained with different settings of the Lokomat (e.g. with more sophisticated settings such as asymmetrical loading of the legs). We only manipulated the 3 main variables, i.e. treadmill speed, BWS and GF. At present, there is no clear evidence available suggesting that certain settings are more effective than others. During the follow-up period, patients received standard individualized care, and it is therefore no surprise that the analyses of the follow-up measurements did not reveal differences between groups in gains either.

Lack of power may be a concern in this study as the sample size is limited. However, effect sizes for the differences in gains for the intervention period were small for the difference between groups after the intervention period at wk10. In this regard it is interesting to note that effect size seems to be higher at follow-up. This could also be due to changes in the sample due to drop-outs. An additional analysis (not reported in results) with only the patients who completed the measurements at wk36 revealed that effect size (r) for the differences at wk10 in walking speed was 0.22 indicating small to moderate effect. Possibly this is an indication that characteristics of the patients who dropped out of the study were different from the patient who remained included. However, analyses of the differences at baseline for time after stroke, walking speed, FAC, BBS, RMI and FM did not reveal significant differences between drop-outs and patients who completed the study.

Presently, seven randomized controlled studies have been published in literature on the effectiveness of improving walking ability using the Lokomat device after stroke.[11,14-19] Westlake et al.[18] and Horby et al.[11] compared the effectiveness of Lokomat therapy with manually assisted treadmill training in a chronic group of patients (n=16 and n=48, respectively), whereas, Hidler et al.[16] did the same for a sub-acute group of patients (n=63). Horby et al.[11] and Hidler et al.[16] found larger increments in walking speed and distance walked for the manually assisted treadmill training

group, whereas Westlake et al.[18] did not find any differences in improvements. Another two studies reported an advantage of Lokomat therapy compared to overground therapy[14,17] in terms of recovery of walking ability. Mayr et al.[14] performed a small (n=16) quasi-experimental study (with mostly sub-acute patients, A-B-A or B-A-B design) and found larger gains in walking related outcome measures in the Lokomat phase of their study than in the overground therapy phase. Schwartz et al.[17] performed a larger trial (n=67, all inpatient) and found that a significantly larger percentage of patients reached a FAC score ≥3 in the group of patients training with the Lokomat than in the conventional overground therapy group. Furthermore, Husemann et al.[15] and Chang et al.[19] did not find any differences in improvements in walking ability between Lokomat and conventional overground therapy in their studies (n=30, between 28-200 days after stroke, and n=37, within 1 month after stroke, respectively). Our study did not find any differences in gains in walking ability between Lokomat and conventional therapy, which is in line with results found by Husemann et al.,[15] Westlake et al.,[18] and Chang et al.,[19] but not with those by Horby et al.,[11] Hidler et al.,[16] Mayr et al.[14] and Schwartz et al.[17] The apparent differences in conclusions of these studies may be due to differences in patient population (ability at baseline and time after stroke), differences in frequency of intervention or control therapy or differences in the type of assistance of the robotic orthoses. The results of studies that investigated the effects of Lokomat therapy using less then fully enforced gait pattern,[14,15,19] are in line with results of several RCTs on the effectiveness of BWSTT training reporting similar or slightly more effect for BWSTT compared to overground therapy.[28-31]

However, the overall evidence for a long-term superiority of improvement of walking ability by any intervention is presently rather weak. Unlike our study, many studies did not perform long-term follow-up measurements. Such long term follow-up measurements are of utmost importance in studies on the effectiveness of any therapy after stroke. Several studies, such as the landmark publication of Duncan et al.,[31] showed that patients can experience greater short term gains in walking ability shortly after stroke with intensive therapy (treadmill locomotor training) than with less intensive intervention. Also Veerbeek et al.[32] showed, based on a meta analysis, that increased time spent on exercise of gait in the first 6 month after stroke results in greater improvement. However, it is also known that some patients show gains in walking ability even up till 1 year after stroke.[33] Indeed, the LEAPS study results demonstrate that although a short term difference between effectiveness of therapy was found at 6 month after stroke, the extent of recovery of walking ability one year after stroke was not affected by intervention type.[31] Presently, there are no studies that convincingly show that a particular intervention is better than others in the long run. Dobkin and Duncan[34] therefore correctly concluded that there is no evidence

suggesting that BWSTT and robot assisted therapy provide clear advantages over conventional overground therapy. In future research on the effectiveness of therapy after stroke, study designs should include long term (e.g. >9 month) follow-up measurements, like in our study, to prevent possible premature conclusions about the effectiveness of a therapy.

In conclusion, the clinical implications of the present study are that Lokomat therapy is an alternative for conventional overground physical therapy during the inpatient rehabilitation period for non-ambulatory stroke patients. For now, practical considerations, based on cost-effectiveness or pragmatic arguments, may direct decisions on whether to use the Lokomat or not in rehabilitation practice. Future research should point out whether robotic step trainers can perhaps be used more effectively (e.g. with other settings or assistance of the orthoses,[35] or for particular subgroups of patients only), possibly in combination with other (experimental) therapies.[36,37]

REFERENCES

1. Roerdink, M., Beek, P.J., Understanding inconsistent step-length asymmetries across hemiplegic stroke patients: impairments and compensatory gait. Neurorehabil Neural Repair, 2011. 25(3): p. 253-8.
2. Patterson, K.K., Gage, W.H., Brooks, D., Black, S.E., McIlroy, W.E., Changes in gait symmetry and velocity after stroke: a cross-sectional study from weeks to years after stroke. Neurorehabil Neural Repair, 2010. 24(9): p. 783-90.
3. Belda-Lois, J.M., Mena-del Horno, S., Bermejo-Bosch, I., Moreno, J.C., Pons, J.L., Farina, D., Iosa, M., Molinari, M., Tamburella, F., Ramos, A., Caria, A., Solis-Escalante, T., Brunner, C., Rea, M., Rehabilitation of gait after stroke: a review towards a top-down approach. J Neuroeng Rehabil, 2011. 8: p. 66.
4. Van de Port, I.G., Wood-Dauphinee, S., Lindeman, E., Kwakkel, G., Effects of exercise training programs on walking competency after stroke: a systematic review. Am J Phys Med Rehabil, 2007. 86(11): p. 935-51.
5. Langhorne, P., Bernhardt, J., Kwakkel, G., Stroke rehabilitation. The Lancet, 2011. 377(9778): p. 1693-1702.
6. Moseley, A.M., Stark, A., Cameron, I.D., Pollock, A., Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev, 2005(4).
7. Mehrholz, J., Werner, C., Kugler, J., Pohl, M., Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev, 2007(4).
8. Hesse, S., Teadmill training with partial body weight support after stroke. NeuroRehabilitation, 2008. 23 p. 55-65.
9. Colombo, G., Wirz, M., Dietz, V., Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord, 2001. 39(5): p. 252-255.
10. Hidler, J., Automating activity-based interventions: The role of robotics. The Journal of Rehabilitation Research and Development, 2008. 45(2): p. 337-344.
11. Hornby, T.G., Campbell, D.D., Kahn, J.H., Demott, T., Moore, J.L., Roth, H.R., Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke, 2008. 39(6): p. 1786-92.
12. Colombo, G., Joerg, M., Schreier, R., Dietz, V., Treadmill training of paraplegic patients using a robotic orthosis. Journal of rehabilitation research and development, 2000. 37(6): p. 693-700.
13. Veneman, J.F., Kruidhof, R., Hekman, E.E., Ekkelenkamp, R., Van Asseldonk, E.H., van der Kooij, H., Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng, 2007. 15(3): p. 379-86.
14. Mayr, A., Kofler, M., Quirbach, E., Matzak, H., Frohlich, K., Saltuari, L., Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair, 2007. 21(4): p. 307-14.
15. Husemann, B., Muller, F., Krewer, C., Heller, S., Koenig, E., Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 2007. 38(2): p. 349-54.
16. Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D.D., Kahn, J.H., Hornby, T.G.,

Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair, 2009. 23(1): p. 5-13.
17. Schwartz I., S.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): p. 516-523.
18. Westlake, K.P., Patten, C., Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. J Neuroeng Rehabil, 2009. 6: p. 18.
19. Chang, W.H., Kim, M.S., Huh, J.P., Lee, P.K., Kim, Y.H., Effects of Robot-Assisted Gait Training on Cardiopulmonary Fitness in Subacute Stroke Patients: A Randomized Controlled Study. Neurorehabil Neural Repair, 2011.
20. Peppen R.P.S., v., Kwakkel G., Harmeling-vander Wel B.., Kollen B.J., Hobbelen J.S.M., Buurke J.H. et al., KNGF Clinical Practice Guideline for physical therapy in patients with stroke. Review of the evidence. [Translation 2008]. Nederlands Tijdschrift voor Fysiotherapie, 2004. 2004(114;5 (Suppl)).
21. Horstman, A.M., Beltman, M.J., Gerrits, K.H., Koppe, P., Janssen, T.W., Elich, P., de Haan, A., Intrinsic muscle strength and voluntary activation of both lower limbs and functional performance after stroke. Clin Physiol Funct Imaging, 2008. 28(4): p. 251-61.
22. Twisk, J.W., de Vente, W., The analysis of randomised controlled trial data with more than one follow-up measurement. A comparison between different approaches. Eur J Epidemiol, 2008. 23(10): p. 655-60.
23. Vickers, A.J., Parametric versus non-parametric statistics in the analysis of randomized trials with non-normally distributed data. BMC Med Res Methodol, 2005. 5: p. 35.
24. Van Breukelen, G.J., ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. J Clin Epidemiol, 2006. 59(9): p. 920-5.
25. Field, A., Discovering statistics using SPSS. 2009: Sage Publications Limited.
26. Kollen, B., van de Port, I., Lindeman, E., Twisk, J., Kwakkel, G., Predicting improvement in gait after stroke: a longitudinal prospective study. Stroke, 2005. 36(12): p. 2676-80.
27. Cai, L.L., Fong, A.J., Otoshi, C.K., Liang, Y., Burdick, J.W., Roy, R.R., Edgerton, V.R., Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci, 2006. 26(41): p. 10564-8.
28. Dean, C.M., Ada, L., Bampton, J., Morris, M.E., Katrak, P.H., Potts, S., Treadmill walking with body weight support in subacute non-ambulatory stroke improves walking capacity more than overground walking: a randomised trial. Journal of Physiotherapy, 2010. 56(2): p. 97-103.
29. Ada, L., Dean, C.M., Morris, M.E., Simpson, J.M., Katrak, P., Randomized trial of treadmill walking with body weight support to establish walking in subacute stroke: the MOBILISE trial. Stroke, 2010. 41(6): p. 1237-42.
30. Franceschini, M., Carda, S., Agosti, M., Antenucci, R., Malgrati, D., Cisari, C., Walking after stroke: what does treadmill training with body weight support add to overground gait training in patients early after stroke?: a single-blind, randomized, controlled trial. Stroke, 2009. 40(9): p. 3079-85.
31. Duncan, P.W., Sullivan, K.J., Behrman, A.L., Azen, S.P., Wu, S.S., Nadeau, S.E., Dobkin, B.H., Rose, D.K., Tilson, J.K., Cen, S., Body-Weight–Supported Treadmill Rehabilitation after

Stroke. The new England Journal of Medicine, 2011. 364(21): p. 2026-36.
32. Veerbeek J.M., K.M., Ket J.C.F., Wegen, van E.E.H., Kwakkel, G, Effects of Augmented Exercise Therapy on Outcome of Gait and Gait-Related in the first 6 months after stroke. A meta-analysis. Stroke, 2011. 42: p. 3311-3315.
33. Kwakkel G., K.B.J., Wagenaar R.C., Long term effects of intensity of arm and leg training in stroke patients. J Neurol Neurosurg Psychiatry, 2002. 72: p. 473-479.
34. Dobkin, B.H., Duncan, P.W., Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair, 2012. 26(4): p. 308-17.
35. Schuck, A., Labruyere, R., Vallery, H., Riener, R., Duschau-Wicke, A., Feasibility and effects of patient-cooperative robot-aided gait training applied in a 4-week pilot trial. J Neuroeng Rehabil, 2012. 9(1): p. 31.
36. Zorner, B., Schwab, M.E., Anti-Nogo on the go: from animal models to a clinical trial. Ann N Y Acad Sci, 2010. 1198 Suppl 1: p. E22-34.
37. Rogers, L.M., Madhavan, S., Roth, H., Stinear, J.W., Transforming neurorehabilitation of walking following stroke: the promise of non-invasive brain stimulation--a review. Restor Neurol Neurosci, 2011. 29(6): p. 507-16

Chapter 5

The relationship between balance and knee extensor strength recovery after stroke: a follow-up study

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ABSTRACT

Objective: To study the association between recovery of maximal isometric knee extensor torque of the paretic leg (MVTp) or relative to the non-paretic leg (relMVT) and recovery of balance after stroke.

Design: a longitudinal observational study

Subjects: 23 stroke patients (time post-stroke: 10±6wks).

Methods: Berg Balance Scale (BBS), MVTp and relMVT were assessed at baseline (wk1), wk10 and wk24. Linear regression was used to study i) the association between BBS and MVTp or relMVT, and ii) the association between the change in BBS (ΔBBS) and the change in MVTp or relMVT (ΔMVTp or ΔrelMVTp) over the two intervals in the study period.

Results: BBS, MVTp and relMVT improved significantly ($p<.05$) over both intervals. The correlations between BBS and MVTp and between BBS and relMVT were of medium size [0.34-0.69] and seemed to be higher at later assessments. ΔBBS was significantly related to ΔMVTp and ΔrelMVT over wk1-wk10, but not over wk10-wk24.

Conclusion: The association between balance and paretic knee extensor strength and the association between changes in balance and changes in paretic knee extensor strength is dependent on time of assessment. This may be due to differences between recovery mechanisms of balance and recovery mechanisms of paretic knee extensor strength.

INTRODUCTION

After stroke, weakness of the leg contra lateral to the lesion is one of the most common deficits.[1] Furthermore, balance and walking ability are affected, resulting in (a.o.) disturbed weight distribution during standing, disturbed equilibrium reactions and higher risk of falls during walking related activities.[2-6] Over the past decade(s) emerging evidence suggests that weakness of the paretic leg is a major factor limiting performance of functional activities after stroke. For instance, in cross-sectional studies, significant relationships have been found between weakness of the paretic leg and sit-to-stance ability, standing balance, and walking ability.[3-7] However, these relationships are often assessed at an arbitrary moment in rehabilitation,[8] and therefore these studies ignore that the relationships between weakness and performance of functional activities may not be constant during the course of recovery after stroke.

The relationships between weakness and performance of functional activities may imply that by reducing weakness, performance of functional activities improves. In literature, it is suggested that reductions in weakness may be realized by therapy (e.g. resistance training) and may result in better performance of functional activities after stroke.[1,7,8] The supposition of effectiveness of reducing weakness to improve performance of functional ability can be studied by relating changes in strength of the paretic leg to changes in performance of functional activities.[7] Longitudinal studies in a cohort of patient during (early) rehabilitation will provide valuable information about the relationships between reduction of weakness of the knee extensors of the paretic leg and improvement of performance of functional activity. Such analyses of change scores have not been studied much before. In a prediction study, the changes in strength of the paretic leg have been reported to be longitudinally related to changes in walking ability for a group of stroke patients during the first 52 weeks after stroke.[9] However, it is unclear whether there is a relationship between changes in weakness of the paretic leg and changes in performance of functional activities throughout the rehabilitation process. Knowledge about the time course of these relationships will add to our understanding of the relationship between weakness of the paretic leg and performance of functional activities and may help to optimize therapy during poststroke neurorehabilitation.

Many patients undergoing early inpatient rehabilitation cannot walk independently which make several tests recording performance of functional activities unsuitable. The Berg Balance Scale (BBS) seems a suitable alternative test of performance of a functional activity in this subgroup of patients because balance is important for many gait-related activities 10 and can be assessed in non-ambulatory patients. The first objective of this paper was to study the relationships between BBS and isometric maximal knee extensor strength of the paretic leg, measured at multiple assessments

during inpatient rehabilitation after stroke in a convenience sample of stroke patient. The second objective was to investigate the relationship between changes in BBS and changes in isometric maximal strength of the paretic knee extensors.

METHODS

Subjects and design

The present study was based on a randomized controlled trial investigating the effectiveness of robot-assisted walking compared to conventional therapy in improving walking ability and walking ability related outcome measures in non-independently walking patients during recovery after stroke (trialregister.nl, NTR3210). As we found no significant differences between groups in the effects on improving muscle strength, control of sitting and standing balance, or walking ability, we combined the patient profiles in one sample in the present longitudinal study. Patients entered the study after a first-ever ischemic or hemorrhagic hemispheric stroke. Main inclusion criteria were: no independent walking ability at start of the study, without cardiovascular problems, no other deficits in movement apparatus or severe cognitive and/or communicative problems preventing the ability to follow verbal instructions. All procedures were approved by the local ethics committee and all subjects gave their written informed consent before participation. The study design consisted of 4 measurements and started as soon as possible after admission in the rehabilitation centre (wk1). After this baseline measurement, all assessments were repeated at 10, 24 and 36 weeks after baseline assessment.

Measurements

We chose the Berg Balance Scale (BBS) as a measure of performance of functional activities, because it can be assessed in patients undergoing early inpatient rehabilitation who cannot walk independently, in contrast to most walking ability measures. The BBS consists of 14 test items, scored on an ordinal five-point scale (0–4), with the scores of all items summed. Below a score of 45, stroke patients are relatively more at risk of falls during walking.[1] BBS is a measure to assess dynamic and static 'standing balance'.[11]

We assessed the maximal isometric voluntary torque of the paretic knee extensors (MVTp) and of the non-paretic knee extensors (MVTnp) using a custom-built strength measuring device (Lower EXtremity System, LEXS), in which unilateral maximal isometric voluntary contractions of the knee extensors were performed (Figure 1).4,5,12,13 Subjects were seated with a hip angle of 100 ° (180° being fully extended hips) and knee angle of 60° (0°= full extension). The lower leg was strapped tightly to a force transducer (KAP, E/200 Hz, Bienfait B.V Haarlem, The Netherlands, range:

0–2 kN) just above the ankle. The distance between the lateral femoral epicondyle and a fixed point at the force transducer was measured representing the external moment arm. A hip belt was fixed tightly to avoid changes in hip and knee angle during contractions and a trunk belt was used for stabilization. Subjects were asked to maximally generate isometric knee extensions for 2 to 4 seconds to determine maximal voluntary knee extension torque. After some practice attempts, at least two to a maximum of five successful attempts were allowed. Force was visualized in real time on a computer screen along with the maximum value achieved up to that trial. Subjects were encouraged to exceed their previously achieved maximal value. Maximal voluntary torque (Nm) was determined as the peak force (highest value of all attempts) multiplied by the external moment arm.

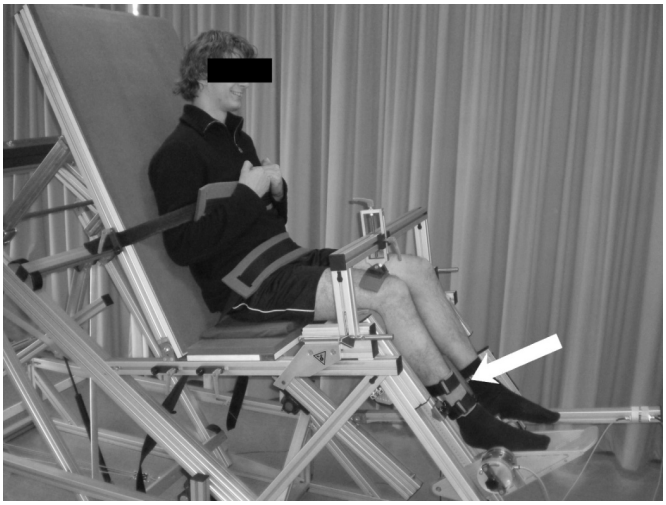

Figure 1: Lower extremity system, with the white arrow indicating the location of the force transducer

Data analysis

Descriptive characteristics of the patients collected at baseline were reported as means with standard deviation (SD). Three observations of the isometric knee extension measurements were imputed by taking the average of the preceding and the following assessments; for one patient at wk 10 and for two patients at wk 24. The isometric strength of the paretic leg expressed in Nm, although often used in literature, does not account for inter-individual differences in maximal strength of the knee extensors. To correct for these inter-individual differences, we calculated the relative isometric knee extensor strength (relMVT) as the percentage of unilateral maximal isometric voluntary torque of the paretic leg (MVT_p) relative to the unilateral maximal isometric voluntary torque of the non-paretic leg (MVT_{np}).

Subsequently we calculated the individual change scores (Δ-scores) for BBS and MVT_p and relMVT. For a valid comparison at different assessment moments, the subject group needs to be the same for all measurements, i.e. we needed a complete data set. Because there was a substantial number of missing values for the last assessment (at wk 36, less than 50% of assessments was available) only the first three assessments were analyzed. Therefore, we only used the data of the 23 patients (out of 30) with a complete set of data for the first 3 assessments. Using paired t-tests, we studied whether BBS and strength scores (MVT_p and relMVT) significantly changed over time. Using linear regression we calculated the regression coefficient for MVT_p explaining BBS at each assessment. Similarly, linear regression was used to calculate the regression coefficient of ΔMVT_p explaining ΔBBS over each assessment interval. The linear regression analyses were then performed again with relMVT and ΔrelMVT as the independent variable. We tested whether outcome variables were approximately normally distributed using Kolmogorov-Smirnov test. For all tests, a 2-tailed significance level of .05 was used. All statistical procedures were performed using IBM SPSS version 20.

RESULTS

The Subject characteristics are shown in Table 1. Table 2 shows means and standard deviations as measured during the assessments at wk1, wk10 and wk24. BBS and MVT_p were normally distributed at all assessments. BBS, MVT_p and relMVT increased significantly over the interval of wk1-wk10 ($p<0.000$, $p<0.011$ and $p<0.014$ respectively, Table 2) and wk10-wk24 ($p<0.000$, $p<0.001$ and $p<0.001$) respectively, Table 2).

Table 1: Patient characteristics at baseline

Characteristic	Total
Gender: women/men	11/12
Stroke hemisphere: left/right	15/8
Type of stroke (ischemic/hemorrhagic)	14/9
Age (± SD) (in yrs.)	54 ± 10
Time after stroke (in weeks ± SD)	10 ± 6

SD=standard deviation

Table 2: Means and standard deviations at all assessments

	Wk1	Wk10	Wk24
BBS (± SD)	18 ± 11	33 ± 14	37 ± 15
MVT_p (± SD) in Nm	39 ± 29	51 ± 29	64 ± 32
relMVT(± SD) in %	27 ± 18	34 ± 17	40 ± 18

	Wk1-wk10	Wk10-wk24
ΔBBS (± SD)	14.3 ± 9.7*	4.2 ± 3.7*
ΔMVT_p (± SD) in Nm	12.2 ± 21.1*	12.6 ± 15.4*
ΔrelMVT (± SD) in %	6.9 ± 12.5*	5.9 ± 7.7 *

BBS=Berg Balance Score, MVTp= knee extension strength of the paretic leg, relMVT= maximal isometric knee extension strength of the paretic leg relative to the non-paretic leg, SD=standard deviation, ΔBBS= change in BBS, ΔMVTp=change in MVTp, ΔrelMVT=change in relMVT, * significant improvement (p<.05)

Table 3 shows the coefficients of the linear regression models of BBS explained by MVT_p at w1, wk10 and wk24 (Figure 2). The results indicate a significant relationship between BBS and MVT_p at wk10 and wk24, but not at wk1. The size of the regression coefficient seems to increase over time and the correlation coefficients increase accordingly. The coefficient for relMVT show similar overall results. Moreover, the model with relMVT explains more variance in BBS than the model for MVT_p.

Table 3: Linear regression models for BBS and MVTp at assessments wk1, wk10 and wk24

Dependent variable	Independent variable	Regression Coefficient	SE	Correlation	P-value
BBS at wk1	MVT_p	0.130	0.077	0.344	0.108
BBS at wk10	MVT_p	0.242	0.095	0.487	0.018
BBS at wk24	MVT_p	0.306	0.079	0.646	0.001
BBS at wk1	relMVT	0.278	0.116	0.462	0.026
BBS at wk10	relMVT	0.479	0.155	0.559	0.006
BBS at wk24	relMVT	0.599	0.137	0.690	0.000

BBS=Berg Balance Score, MVT_p= maximal isometric knee extension strength of the paretic leg, relMVT= maximal isometric knee extension strength of the paretic leg relative to the non-paretic leg, SE= standard error

Table 4 shows the coefficients of the linear regression models of ΔBBS explained by ΔMVT_p and ΔrelMVT for the interval of wk1-wk10 and wk10-wk24 (Figure 2). The results indicate a significant relationship between ΔBBS and ΔMVT_p over the interval of wk1-wk10, whereas there is no significant relationship over the interval of wk10-

wk24. Similarly, the results indicate a significant relationship between ΔBBS and ΔrelMVT over the interval of wk1-wk10, whereas there is no significant relationship over the interval of wk10-wk24.

Table 4: Linear regression models for ΔBBS and ΔMVTp over the intervals of wk1-wk10 and wk10-wk24

Dependent variable	Independent variable	Regression Coefficient	SE	Correlation	P-value
ΔBBS over wk1-wk10	ΔMVTp	0.248	0.085	0.537	0.008
ΔBBS over wk10-wk24	ΔMVTp	-0.049	0.046	-0.226	0.299
ΔBBS over wk1-wk10	ΔrelMVT	0.347	0.152	0.446	0.033
ΔBBS over wk10-wk24	ΔrelMVT	-0.101	0.092	-0.233	0.284

ΔBBS= change in BBS per week, ΔMVTp=change in maximal isometric knee extension strength of the paretic leg, ΔrelMVT=change in maximal isometric knee extension strength of the paretic leg relative to the non-paretic leg, SE= standard error

DISCUSSION

In this study we demonstrated significantly positive relationships between BBS and MVT_p and between BBS and relMVT during rehabilitation after stroke. Moreover, we showed that these relationships were stronger at follow-up assessments. Furthermore, we showed that changes in balance (ΔBBS) were positively and significantly associated with changes in isometric maximal strength of the paretic knee extensors (ΔMVT_p or ΔrelMVT) over the interval of wk1-wk10, but not over the interval of wk10-wk24.

Relationship between BBS and MVT_p and between BBS and $relMVT_p$

Our results are in line with literature suggesting that the maximal isometric strength of the paretic knee extensors is significantly related to patient's ability to perform gait and gait related activities during the more chronic phases after stroke.[14] Moreover, it is in line with longitudinal studies, in which strength of the paretic leg was associated with balance and walking ability.[11] The relationship between BBS and MVT_p at wk1, however, was not significant. This non-significant relationship might be due to large variation between individuals in terms of maximal strength which were already present before the stroke (e.g. differences in height, sex or intrinsic strength generating capacity of the knee extensors). Indeed, when corrected for the inter-individual differences in absolute strength (or force/torque) of the non-paretic leg by using the relMVT, we did find a significant relationship. Moreover, the model with relMVT also provides more explained variance indicating its superiority

over the model with MVT_p. Our results also indicate that at follow-up assessments, the relationship between BBS and MVT_p is stronger, which is in accordance with a study showing increases of the explained variance of walking speed by strength of the paretic leg at a follow-up assessment compared to that at the first assessment of the study.[15] These findings can be explained by previously suggested mechanisms of recovery after stroke. First of all, the amount of individual reductions in weakness is related to the initial impairment.[16] Secondly, it is commonly believed that reductions in impairment measures (like MVT_p or relMVT) are associated with true recovery, whereas improvements in performance of functional activities (like BBS) are associated with true recovery, compensation strategies, or a combination of these.[16] Therefore, BBS will most likely improve relatively more compared to MVT_p or relMVT. Consequently, at a follow-up assessment of the relationship (regression coefficient) between BBS and MVT_p, the regression coefficient will be higher. Researchers need to take this into consideration in any study which relates strength measures with performance of functional activities measures.

Relationship between ΔBBS and ΔMVT_p or ΔBBS and $\Delta relMVT_p$

The positive and significant relationship between ΔBBS and ΔMVT_p or ΔrelMVT over the interval of wk1-wk10 are in line with literature showing that in rehabilitation after stroke, changes in strength of the paretic leg are longitudinally related to changes of walking ability.[9] From a statistical point of view, we expected that the correlation coefficient between ΔBBS and ΔMVT_p would be lower during wk10-wk24 compared to wk1-wk10 because we anticipated smaller changes over interval wk10-wk24 compared to wk1-wk10 with similar measurement error, thus obscuring the 'real' relationship. Indeed, we found no significant relationship between ΔBBS and ΔMVT_p nor between ΔBBS and ΔrelMVT over wk10-wk24. However, since the improvements in strength of the isometric knee extensors were, contrary to our expectations, relatively large and the improvements in BBS over wk10-wk24 still significant other explanations for the change in the relationships between weakness and functional performance may be suggested. One explanation may relate to different mechanisms through which reductions in weakness and performance of functional activities are mediated in the two intervals. According to literature, early after stroke, structural changes occur in the brain due to spontaneous recovery.[17] It is possible that over interval wk1-wk10, improvements in voluntary activation were the main mechanism responsible for the reductions in weakness, whereas over interval wk10-wk24, improvements in cross-sectional area of the knee extensors may have occurred thus reducing weakness. Possibly, reductions in weakness due to improvement in voluntary activation are related to improvements in performance of functional activities, whereas reductions in weakness due to increased cross-sectional area are not, or less associated with

improvements in performance of functional activities. Alternatively, it is possible that inter-individual differences in how balance is learned, possibly through differential use of compensatory strategies to maintain balance have lead to the non-significant relationship between ΔBBS and ΔMVT_p or ΔBBS and ΔrelMVT over wk10-wk24. Moreover, patients may have improved function in other muscles of the paretic leg, or patients may have improved in sensory function which might have resulted in the non-significant relationship between ΔBBS and ΔMVT_p or between ΔBBS and ΔrelMVT over wk10-wk24. However, we do not have information about how strength of other muscles or sensory function has changed during this study, nor do we know whether the changes we observed in this study were therapy induced or spontaneous. Such analyses are useful in understanding the relationship between changes in impairments and changes in performance of functional activities. For example, it may be particularly useful in studying the effectiveness of improving strength through resistance training to improve performance of functional activities. Because we did not perform a strengthening intervention, this study does not provide indications on whether strength training should be performed during rehabilitation or not.

In line with the literature we recognize that, in our study, time after stroke is an independent covariate for the amount of recovery after stroke.[18] Preliminary analyses, however, only showed a significant correlation between time after stroke and MVT_p at wk24, so we think we can be fairly confident that in our sample, time after stroke was not a major issue. We, nevertheless, recommend that to improve comparability of patients in terms of biological mechanisms of recovery, ideally, in future studies with similar goals, patients are enrolled in the study at the same time after stroke. Moreover, this may decrease the inter-individual differences, thereby improving the estimates of the models.

Furthermore, in the analyses, ceiling effects should be considered, because it might be possible that patients reached the maximum test score for a particular test. In our study, results were probably not due to ceiling effects in the assessments tools used in this study as no patient reached the maximum possible BBS values before wk24. Another limitation of this study is that MVT_p and relMVT are measures of knee extensor strength only, which, besides not differentiating between intrinsic strength capacity and the ability to maximally activate the knee extensors, obviously lacks information about other leg muscles in the paretic leg which also lacks the dynamic qualities of strength generation. Moreover, since individual patterns of recovery in terms of impairments and disability are heterogeneous, and are influenced by background variables of which some have been identified such as age[9] or therapy intensity[19] extrapolation of our results may be erroneous. Needless to say, general claims on the relationship between impairment and performance of functional activities for the whole stroke population based on our study should be made with

caution. Finally, the size of the sample and inclusion criteria of the patients limits generalizability to the general stroke population.

We conclude that the relationships between weakness of the paretic knee extensors and balance are not constant during the course of recovery after stroke, possibly due to compensation strategies during maintaining balance. Other relationships between variables measuring an aspect of weakness of the paretic leg and variables of performance of functional activities might show similar changes over time. Furthermore, apparently, reductions in weakness of the paretic knee extensors are not always associated with improvements in balance. Further research is necessary to investigate how the reductions in weakness of the paretic leg relate to improvements in performance of functional activities. For instance, it seems valuable to investigate how improved voluntary activation or improvements in cross-sectional area relate to improved performance of functional activities. We recommend that these future studies use analyses of the changes in the variables under study.

REFERENCES

1. Pak, S., Patten, C., Strengthening to promote functional recovery poststroke: an evidence-based review. Top Stroke Rehabil, 2008. 15(3): p. 177-99.
2. De Haart, M., Geurts, A.C., Huidekoper, S.C., Fasotti, L., van Limbeek, J., Recovery of standing balance in postacute stroke patients: a rehabilitation cohort study. Arch Phys Med Rehabil, 2004. 85(6): p. 886-895.
3. Bohannon, R.W., Knee extension strength and body weight determine sit-to-stand independence after stroke. Physiother Theory Pract, 2007. 23(5): p. 291-7.
4. Horstman, A.M., Beltman, M.J., Gerrits, K.H., Koppe, P., Janssen, T.W., Elich, P., de Haan, A., Intrinsic muscle strength and voluntary activation of both lower limbs and functional performance after stroke. Clin Physiol Funct Imaging, 2008. 28(4): p. 251-61.
5. Gerrits, K.H., Beltman, M.J., Koppe, P.A., Konijnenbelt, H., Elich, P.D., de Haan, A., Janssen, T.W., Isometric muscle function of knee extensors and the relation with functional performance in patients with stroke. Arch Phys Med Rehabil, 2009. 90(3): p. 480-7.
6. Bohannon, R.W., Walsh, S., Association of paretic lower extremity muscle strength and standing balance with stair-climbing ability in patients with stroke. Journal of Stroke and Cerebrovascular Diseases, 1991. 1(3): p. 129-133.
7. Patten, C., Lexell, J., Brown, H.E., Weakness and strength training in persons with poststroke hemiplegia: rationale, method, and efficacy. J Rehabil Res Dev, 2004. 41(3A): p. 293-312.
8. Bohannon, R.W., Muscle strength and muscle training after stroke. J Rehabil Med, 2007. 39(1): p. 14-20.
9. Kollen, B., van de Port, I., Lindeman, E., Twisk, J., Kwakkel, G., Predicting improvement in gait after stroke: a longitudinal prospective study. Stroke, 2005. 36(12): p. 2676-80.
10. Veerbeek, J.M., Van Wegen, E.E., Harmeling-Van der Wel, B.C., Kwakkel, G., Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. Neurorehabil Neural Repair, 2011. 25(3): p. 268-74.
11. Van Nes, I.J., van Kessel, M.E., Schils, F., Fasotti, L., Geurts, A.C., Kwakkel, G., Is visuospatial hemineglect longitudinally associated with postural imbalance in the postacute phase of stroke? Neurorehabil Neural Repair, 2009. 23(8): p. 819-24.
12. Horstman, A., Gerrits, K., Beltman, M., Janssen, T., Konijnenbelt, M., de Haan, A., Muscle function of knee extensors and flexors after stroke is selectively impaired at shorter muscle lengths. J Rehabil Med, 2009. 41(5): p. 317-21.
13. Horstman, A.M., Gerrits, K.H., Beltman, M.J., Koppe, P.A., Janssen, T.W., de Haan, A., Intrinsic properties of the knee extensor muscles after subacute stroke. Arch Phys Med Rehabil, 2010. 91(1): p. 123-8.
14. Bohannon, R., Williams Andrews, A., Relationship between impairments and gait performance after stroke: a summary of relevant research. Gait Posture, 1995. 3(4): p. 236-240.
15. Nakamura, R., Watanabe, S., Handa, T., Morohashi, I., The Relationship between Walking Speed and Muscle Reflexes for Knee extsnion in Hemiparetic Stroke Patients: a follow-up study. Tohoku, 1988.
16. Prabhakaran, S., Zarahn, E., Riley, C., Speizer, A., Chong, J.Y., Lazar, R.M., Marshall, R.S., Krakauer, J.W., Inter-individual variability in the capacity for motor recovery after ischemic

stroke. Neurorehabil Neural Repair, 2008. 22(1): p. 64-71.
17. Kwakkel, G., Kollen, B.J., Wagenaar, R.C., Understanding the pattern of functional recovery after stroke facts and theories. Restorative Neurology and Neuroscience, 2004. 22: p. 281-299.
18. Kwakkel, G., Kollen, B., Twisk, J., Impact of time on improvement of outcome after stroke. Stroke, 2006. 37(9): p. 2348-53.
19. Veerbeek J.M., K.M., Ket J.C.F., Wegen, van E.E.H., Kwakkel, G, Effects of Augmented Exercise Therapy on Outcome of Gait and Gait-Related in the first 6 months after stroke. A meta-analysis. Stroke, 2011. 42: p. 3311-3315.

Chapter 6

The effect of robotic gait training on the cardiorespiratory system in incomplete spinal cord injury

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ABSTRACT

The objectives were to investigate the effect of robot-assisted gait training on cardiorespiratory fitness in subjects with motor incomplete spinal cord injury and to examine the exercise intensity of robotic walking and compare this with recommended guidelines. Ten patients followed a 24-session training program with a robotic gait orthosis in addition to physiotherapy sessions completed within 10-16 weeks. Cardiorespiratory fitness was determined in a graded arm crank exercise test before and after the training program. To assess the intensity of robot-assisted walking, oxygen consumption ($\dot{V}O_2$) and heart rate (HR) were measured during a training session early in and at the end of the training program and exercise intensity measures (%$\dot{V}O_2$ reserve ($\dot{V}O_2$R), %HR reserve (HRR), Metabolic Equivalents (METs)) were calculated. Whereas no changes were found in peak $\dot{V}O_2$, the resting and submaximal HR at a constant work load were significantly lower after training. Most subjects exercised at low intensity (<30%$\dot{V}O_2$R, <30%HRR, <3.0 METs) and only two subjects exercised at moderate intensity (>3.0 METs). In spite of the low exercise intensity of the training program and no changes in peak $\dot{V}O_2$, robot-assisted gait training induced some improvement in cardiorespiratory fitness, as suggested by a lower resting and submaximal HR.

INTRODUCTION

Physical inactivity is commonly reported in the spinal cord injury (SCI) population,[1] and is a major risk factor for developing cardiovascular disease (CVD).[2,3] Being physically active can prevent CVD and a wide range of other medical conditions such as diabetes and obesity.[4-6] Therefore, interventions to promote physical activity in the SCI population are becoming increasingly important. Traditional exercise modes to improve physical fitness for the SCI population are arm exercise in a wheelchair or using an arm ergometer and leg exercise with functional electrical stimulation (FES). However, the prevalence of shoulder pain, mostly as a result of overuse, is very high in wheelchair users.[7-9] Therefore, an exercise modality without a repetitive use of upper extremities may be preferable. By using FES exercise, the large muscles of the legs can be activated which can lead to a wide range of fitness and health benefits.[10-11] However, about half of the population with SCI[12] have incomplete lesions, which makes the application of FES painful for many of these individuals. As an alternative, robot-assisted gait training with the Lokomat was introduced[13] as a form of aerobic exercise for these individuals with incomplete spinal cord injury (iSCI).

The Lokomat is a device consisting of two robotic arms and a treadmill with a body weight support system. The robotic arms can be attached to the patient's legs and the body weight is supported by a body weight support system while walking on the treadmill.[14,15] Speed, body-weight support and amount of assistance can be adjusted to individual ability in order to create a challenging environment where patients can practice stepping. Most studies investigating robot-assisted gait training in iSCI focused on the effectiveness of improving neurologic and motor function and concluded that it is an appropriate therapy for improving walking ability.[16-17] Although there is some knowledge with regard to the cardiovascular effects of body weight supported treadmill training with manual assistance,[13,18-21] little is documented about the cardiorespiratory effects of robot-assisted gait training.

Promising results with regard to cardiovascular effects of robot assisted therapy[22-25] in SCI population have been reported. A recent cross-sectional study by Jack et al.[24] showed that, with vigorous active participation of patients, a substantial increase in heart rate (HR) and oxygen consumption ($\dot{V}O_2$) can be achieved. However, without the voluntary activity of the patient (i.e. passive walking) exercise intensity (HR and $\dot{V}O_2$) was much lower and probably insufficient to stress the cardiopulmonary system according to the levels of intensity for aerobic training as recommended by the American College of Sports Medicine (ACSM). Recently, by the use of more sophisticated controllers of the orthoses, gait patterns during robotic walking are less prescribed and more variation is possible. These new controllers allow active participation of patients in the kinematics of locomotion, which may be more effective for motor learning.[26-27] However, the effects on the cardiorespiratory system have

not been studied yet. Furthermore, little has been documented about longitudinal changes in cardiopulmonary fitness by Lokomat therapy in SCI patients.[13] Therefore, this study had two goals. The primary purpose of this study was to investigate the effect of a period of active robot-assisted gait training on cardiopulmonary fitness in subjects with a motor incomplete SCI. The secondary purposes of the study were to examine the exercise intensity of robotic walking and to compare this to the recommended guidelines for exercise intensity of the ACSM.

METHODS

Subjects

Ten subjects with a motor iSCI participated in this study (Table 1). The inclusion criteria were: paraplegia or tetraplegia as a result of a motor iSCI (ASIA Impairment Scale C, D[28]), minimum age of 18 years, height between 150 – 195 cm, maximum body mass of 115 kg. The limiting height and mass were necessary because of the design of the Lokomat device. The exclusion criteria were: medical complications, such as uncontrolled cardiac dysrhythmia and other unstable cardiovascular problems, severe skeletal problems such as osteoarthritis or recent fractures of the lower limbs, severe cognitive and/or communicative disorders, other neurological and/or psychiatric disorders, severe spasticity, open wounds or unhealed skin, thrombosis, pneumonia, other problems that make it impossible to accomplish the tasks. Information about the type and location of the lesion was provided by a clinical evaluation by a physician. After a detailed explanation of the purpose and the protocol of the experiments, all subjects signed an informed consent. The study was approved by the ethics committee of the VU University Medical Center Amsterdam.

Study design

A single-group pretest-posttest design was used to investigate whether cardiorespiratory fitness improved during the course of an intervention with robot-assisted gait training and additional physical therapy. This pretest-posttest trial is used to assess possible effects of this intervention, as it is an essential step before setting up a randomized control trial.[29] Cardiorespiratory fitness was evaluated using a graded arm crank exercise test performed at baseline and immediately after the training program. To examine the intensity of the training program, $\dot{V}O_2$ and HR were measured during a training session at the start and at the end of the training program.

Table 1. Subject characteristics at baseline.

Subject ID	Sex	Age (years)	Height (cm)	Body mass (kg)	Lesion level	Time post-injury (years)	ASIA	LEMS
C1	M	52	185	79	L1 - L2	9	C	11
C2	F	31	161	50	T9 - T10	17	C	25
C3	F	44	170	96	T8	35	C	12
C4	M	35	173	76	T5	1	C	19
C5	F	33	166	63	C5 - T1	<1	C	13
C6	F	60	173	78	T4	5	C	10
D1	F	67	172	73	T1 - C1	8	D	41
D2	M	64	168	114	C5 - C6	<1	D	50
D3	F	34	172	60	T7	8	D	31
D4	M	63	180	83	C3	5	D	44
Mean		49	172	77				26
SD		14	7	17				15

SD = standard deviation, M = male, F = female, ASIA = American Spinal Injury Association Impairment Scale,[28] LEMS = Lower Extremity Motor Score.

Training program

The training program consisted of 24 training sessions with a Lokomat device (Hocoma AG, Volketswil, Switzerland) with additional physical therapy sessions completed within 10 to 16 weeks. Training sessions were performed two or three times per week with at least one day of rest between two sessions. Each robotic training session lasted 60 minutes and contained 20 to 40 minutes walking time. Subjects trained with an individually adapted walking speed, body weight support (BWS) and robotic support (guidance force (GF)) in a way that he/she was able to walk comfortably for about 30 minutes. Training settings were adjusted individually by optimizing BWS, speed and GF as long as the training settings were tolerated by the patient. The additional physical therapy sessions consisted of usual home-based therapy at a local physical therapy practice or therapy in the rehabilitation center, which focused mainly on walking ability. This additional physical therapy was not protocolized.

Arm crank exercise test

Each subject performed a discontinuous progressive graded exercise test on an Angio arm ergometer (Lode BV, Groningen, The Netherlands) to assess cardiorespiratory function. The exercise tests were carried out by an experienced researcher. Subjects were asked to avoid food/caffeine/alcohol intake 2 hours prior

to the exercise tests. Before the exercise test, resting values for $\dot{V}O_2$ and HR were measured during five minutes of seated rest. In recorded test data, there were no signs of hyperventilation or signs for abnormal electrocardiogram (ECG). The exercise protocol consisted of a minimum of three blocks of three-minute arm pedalling at 60 rpm. The increase in work load was individually set by the researcher such that subjects needed a minimum of three exercise blocks to reach their peak performance. The estimation was based on the exercise performance (HR) of the first exercise block. One minute of rest after each block was included to facilitate the measurements for an additional study (recordings of the ECG and impedance cardiogram (ICG), see Meijer et al.[30]). Subjects were verbally encouraged to exercise to exhaustion. The exercise test was ended when a subject was not able to continue pedalling at 60 rpm due to exhaustion or when the subject indicated that he/she wanted to stop. During the whole exercise test, $\dot{V}O_2$ was continuously monitored with a spirometer (Oxycon Alpha or Oxycon Mobile, Jaeger, Bunnik, The Netherlands) to measure $\dot{V}O_2$. $\dot{V}O_2$ was measured breath-by-breath and averaged over 5-s intervals. Throughout testing, HR was monitored by a Polar sport tester (Polar RS400/Polar RS800 and Polar WearLink belt) with a 5-s recording rate. In cases the Polar sport tester provided incorrect values of heart rates due to technical problems, the recorded ECG was used to calculate the proper heart rates. Pre- and posttest were executed following the same procedure. An example of the experimental setup of the exercise test is depicted in Figure 1.

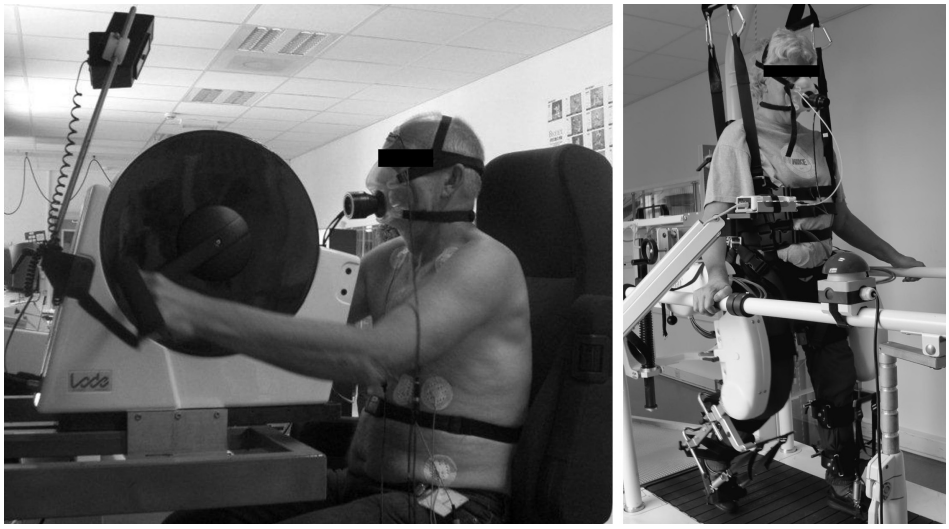

Figure 1: Experimental setup of the arm crank exercise test (left) and of the tested training sessions (right).

Robotic walking tests

The first measurement was performed during one of the early therapy sessions (6th, 7th or 8th) when patients had become accustomed to walking in the device. The last measurement was performed during the 23rd or 24th training session. The timing of assessment was predominantly based on practical reasons (e.g. availability of subjects and measuring equipment). During both measurements, $\dot{V}O_2$ and HR were measured in the same way as during the arm crank exercise test. Prior to the training sessions, resting values of $\dot{V}O_2$ and HR were measured during five minutes of rest in a sitting position. The experimental setup is depicted in Figure 1. The procedure of both tested training sessions was as follows:

1. Subjects performed a 5-10-min warm up to familiarize with the equipment and to warm up the legs.
2. Part 1: walking at an individually standardized walking condition
   During the first part of the training session, individually adapted walking speed, BWS and GF were kept constant for at least four minutes to obtain steady state values for $\dot{V}O_2$ and HR. During both tested training sessions, the individually standardized walking settings of the robotic support were identical for each subject.
3. Part 2: exercise intensity of robotic walking
   During the last part of the training session, walking speed, BWS and GF were adjusted in a way, representative of a regular training session at that moment, to measure the exercise intensity.

Outcome measures cardiorespiratory fitness

Nine outcome measures were used from the graded arm crank test. Resting $\dot{V}O_2$ and resting O_2 pulse ($\dot{V}O_{2rest}$,and O_2pulse_{rest}, respectively) were determined as the average over the last 60 seconds of quiet sitting. Submaximal $\dot{V}O_2$ and submaximal O_2 pulse ($\dot{V}O_{2submax}$, and O_2pulse_{submax}, respectively) were determined as the average of the last 30 seconds of block two of the arm crank exercise test. During this second block, subjects exercised at a submaximal intensity with a constant work load. Peak $\dot{V}O_2$ and peak O_2 pulse ($\dot{V}O_{2peak}$,and O_2pulse_{peak}, respectively) were determined as the average of the last 20 seconds of the last block of the arm crank exercise test. Furthermore, the lowest obtained heart rate during five minutes of seated rest was used as HR_{rest}, submaximal HR (HR_{submax}) was determined as the average of the last 30 seconds of block two and peak HR (HR_{peak}) was the highest heart rate found in the last block. O_2 pulse as a measure for cardiovascular efficiency was determined according to the following equation 1:

$$O_2 \text{ pulse (ml/beat)} = \frac{\text{oxygen uptake (ml/min)}}{\text{heart rate (bpm)}} \quad (1)$$

A higher O_2 $pulse_{submax}$ after the training programme would therefore indicate an improvement in cardiovascular efficiency. Changes in submaximal $\dot{V}O_2$ ($\dot{V}O_{2submax}$) at a given workload would reflect changes in mechanical efficiency (for example due to better coordination of arm muscles).

Outcome measures robotic walking intensity

Nine outcome measures from the robotic walking trials were used for analysis. Resting $\dot{V}O_2$ ($\dot{V}O_{2rest\_robot}$) was determined as the average of the last 60 seconds during seated rest. Resting HR (HR_{rest_robot}) was determined as the lowest obtained heart rate during sitting. Furthermore, the average of values over ten minutes of robotic walking during the last part of the training session were determined ($\dot{V}O_{2robot}$ and HR_{robot}). Finally, steady state values of $\dot{V}O_2$ and HR ($\dot{V}O_{2std}$, HR_{std}), measured during the standardized robotic walking task, were calculated by averaging the last 60 seconds of walking at the specific standardized walking condition. $\dot{V}O_{2robot}$ measures were expressed as a percentage of oxygen uptake reserve (%$\dot{V}O_2$R)[31] and metabolic equivalents (METs)[31] and HR_{robot} was expressed as a percentage of heart rate reserve (%HRR).[31] The %HRR, %$\dot{V}O_2$R and METs were used as measures for the exercise intensity of the training program and were calculated by using the following equations (2 – 4):

$$\%\,HRR = \frac{HR_{robot} - HR_{rest}}{HR_{peak} - HR_{rest}} * 100 \quad (2)$$

$$\%\dot{V}O_2R = \frac{\dot{V}O_{2robot} - \dot{V}O_{2rest}}{\dot{V}O_{2peak} - \dot{V}O_{2rest}} * 100 \quad (3)$$

$$METs = \frac{\dot{V}O_{2robot}}{\dot{V}O_{2rest}} \quad (4)$$

Subsequently, the obtained %HRR, %$\dot{V}O_2$R and METs were compared with exercise intensity recommendations for sedentary people.[31] ACSM guidelines for sedentary/extremely deconditioned able-bodied adults recommend training at an intensity of 30 - 45 %HRR or %$\dot{V}O_2$R in order to maintain or improve physical fitness.

Statistical analysis

After checking if the data followed a normal distribution, paired t-tests were used to determine if there were significant differences in resting, submaximal and peak $\dot{V}O_2$, HR and O_2 pulse between both arm crank tests or between both tested training sessions. Means and standard deviations (SDs) were computed (but not all reported) for all outcome measures (Table 2; Table 3). Furthermore, the mean differences (with 95% confidence intervals) were also calculated. All statistical analyses were performed using SPSS version 19.0 for Windows. The significance level was set at 5%.

Table 2: Mean and SD of resting, submaximal and peak values of oxygen uptake ($\dot{V}O_2$), heart rate (HR) and O_2 pulse measured during both arm crank exercise tests (pre- and posttests).

Outcome measures	N	Pretest	Posttest	Difference (post - pre)		
		Mean ± SD	Mean ± SD	Mean and 95% CI	t-value	p-value
Resting values						
$\dot{V}O_{2rest}$ (mL·min-1)	9	247 ± 57	249 ± 61	2 (-29 to 33)	0.147	0.887
HR_{rest} (bpm)	9	78 ± 14	71 ± 12	-7 (-12 to -1)	-2.744	0.025*
O_2pulse_{rest} (mL·beat-1)	9	3.0 ± 0.5	3.3 ± 1.0	0.3 (-0.2 to 0.9)	1.435	0.189
Submaximal values						
$\dot{V}O_{2submax}$ (mL·min-1)	9	750 ± 182	741 ± 209	-9 (-75 to 58)	-0.304	0.769
HR_{submax} (bpm)	9	116 ± 14	108 ± 14	-7 (-13 to -2)	-3.359	0.010*
O_2pulse_{submax} (mL·beat-1)	9	6.5 ± 1.7	6.9 ± 2.1	0.4 (-0.3 to 1.1)	1.427	0.191
Peak values						
$\dot{V}O_{2peak}$ (mL·min-1)	9	1163 ± 407	1207 ± 402	44 (-120 to 208)	0.619	0.553
$\dot{V}O_{2peak}$ (mL·min-1·kg-1)	9	15.7 ± 5.1	16.5 ± 5.7	0.8 (-1.4 to 3.0)	0.835	0.428
HR_{peak} (bpm)	9	152 ± 26	151 ± 28	-1 (-9 to 7)	-0.237	0.819
O_2pulse_{peak} (mL·beat-1)	9	7.8 ± 2.1	7.5 ± 3.0	-0.3 (-1.8 to 1.2)	-0.424	0.683

SD = standard deviation, 95% CI = 95% confidence interval, bpm = beats per minute, * = a significant difference ($p<0.05$) between pre- and post-values.

Table 3: Mean values (± SD) of oxygen uptake ($\dot{V}O_2$) and heart rate (HR) together with the exercise intensity measures determined during a training session at the start (first training) and at the end (last training) of the training program.

Measures	N	First training	Last training	Difference (last – first)		
		Mean ± SD	Mean ± SD	Mean and 95% CI	t-value	p-value
Robotic walking						
$\dot{V}O_{2robot}$ (mL·min-1)	10	536 ± 226	492 ± 203	-44 (-109 to 21)	-1.54	0.159
$\dot{V}O_{2robot}$ (mL·min-1·kg-1)	10	6.8 ± 2.2	6.4 ± 2.2	-0.5 (-1.3 to 0.3)	1.30	0.225
HR_{robot} (bpm)	10	94 ± 13	88 ± 10	-6 (-13 to 2)	-1.73	0.118
$\dot{V}O_{2std}$ (mL·min-1)	10	558 ± 267	453 ± 184	-105 (-215 to 4)	-2.171	0.058
HR_{std} (bpm)	10	94 ± 16	84 ± 9	-10 (-19 to 0)	-2.263	0.050
Exercise intensity						
%$\dot{V}O_2$R	8	23 ± 14	20 ± 13	3 (-9 to 3)	-1.001	0.347
%HRR	7	23 ± 11	14 ± 11	8 (-16 to -0.4)	-2.536	0.044*
METs	10	2.2 ± 0.9	2.1 ± 0.9	-0.1 (-0.4 to 0.1)	-1.366	0.205

SD = standard deviation, 95% CI = 95% confidence interval, V̇O2robot and HRrobot = V̇O2 and HR during robotic walking, V̇O2std and HRstd = V̇O2 and HR during standardized robotic walking task, bpm = beats per minute, %V̇O2R = percentage V̇O2 reserve, %HRR = percentage of heart rate reserve, METs = V̇O2robot/V̇O2rest, * = a significant difference ($p<0.05$) between both tested sessions.

RESULTS

Arm crank exercise test

One subject was unable to perform the arm crank exercise test due to inability to pedal with the device. Individual values of HR_{rest}, O_2pulse_{rest}, HR_{submax}, O_2 $ulse_{submax}$, $\dot{V}O_{2submax}$ and $\dot{V}O_{2peak}$ are depicted in Figure 2. Table 2 shows the resting, submaximal and peak values of $\dot{V}O_2$ (absolute and normalized for body mass), HR and O_2 pulse measured during both tests. The t-test showed no significant difference in $\dot{V}O_{2submax}$ between pre- and posttest, but HRsubmax was significantly lower after the training program (Table 2; Figure 2). As a result of a lower submaximal HR at the similar submaximal $\dot{V}O_2$, O_2pulse_{submax} tended to be higher during the posttest. In line with submaximal values, HR_{rest} was significantly lower at posttest compared to the pretest.

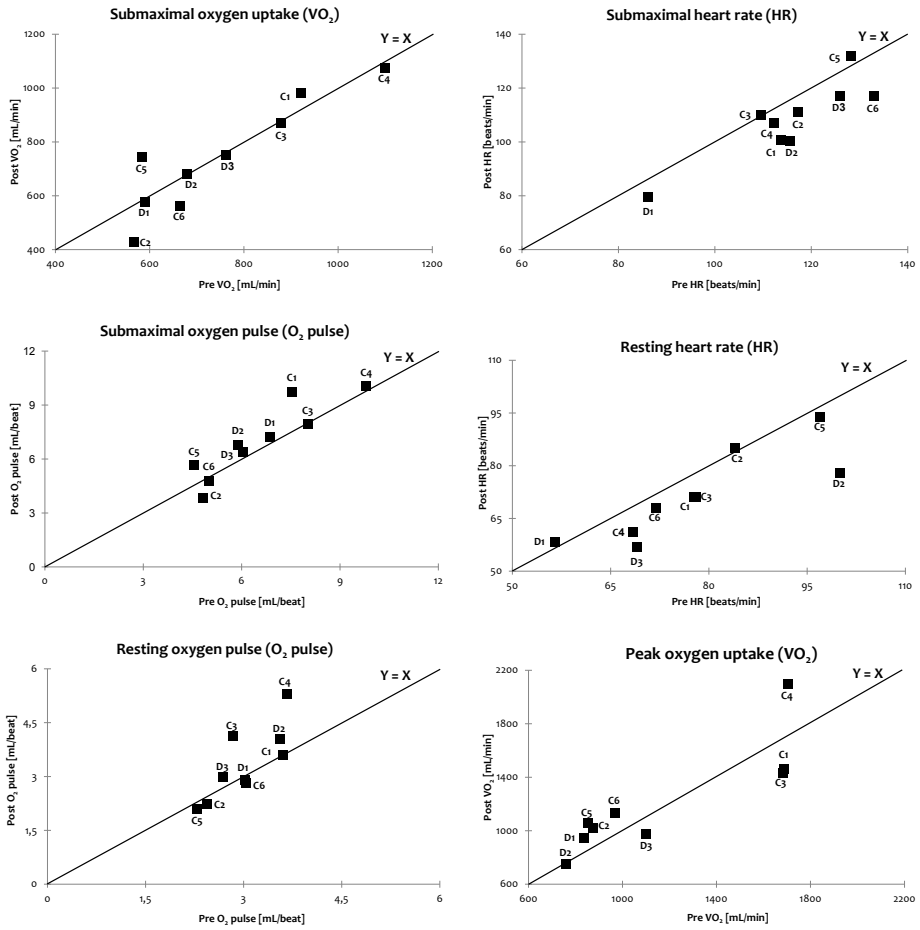

Figure 2. Individual values of resting HR (upper-left), resting O_2 pulse (upper-right), submaximal HR (middle-left), submaximal O_2 pulse (middle-right), submaximal $\dot{V}O_2$ (bottom-left) and peak $\dot{V}O_2$ (bottom-right) measured during both arm crank exercise tests (pre- and posttest). The line of identity (y = x) is also shown in the graphs. Resting and submaximal heart rate at posttest were significantly lower compared to pretest. No significant changes were found in resting O_2 pulse, submaximal O_2 pulse, submaximal $\dot{V}O_2$ and peak $\dot{V}O_2$.

Robotic walking

No changes were found in $\dot{V}O_{2robot}$ and HR_{robot} between first and last tested training sessions (Table 3). Although not significant ($p<0.1$), almost all subjects had lower $\dot{V}O_{2std}$ and HR_{std} during the standardized robotic walking task at the last training session compared to the first tested training session. Two subjects (D2 and D4) obtained their peak $\dot{V}O_2$ and HR during robotic walking instead of the arm crank exercise test. Therefore, it was not possible to calculate valid values for %HRR and

%$\dot{V}O_2$R of robotic walking for these subjects. Also, the %HRR of the last tested training session of subject D1 was excluded from the analyses, because during the whole training session, the heart rates of subject D1 were substantially higher compared to all other tests resulting in a much higher %HRR. For the remaining individuals no significant differences in %$\dot{V}O_2$R and METs were found between the start and the end of the training program (Table 3). However, %HRR was significantly lower at the last training session compared to first tested session.

Individual results of %$\dot{V}O_2$R, %HRR and METs obtained at both tested training sessions are presented in Figure 3. Based on the %$\dot{V}O_2$R measured at the first tested training session, only subjects C3, C4 and D1 met the recommended guidelines of exercise intensity. During the last training session, subjects C3, D1 and D3 achieved a %$\dot{V}O_2$R above the minimum recommended value of 30% $\dot{V}O_2$R. In the same way, it is illustrated that at the start of the training program the %HRR of subjects C3, C6 and D1 was above the recommended guidelines. At the end of the training program, only subject C3 exercised at an intensity above 30% HRR. $\dot{V}O_2$ during robotic walking was one to three times higher than $\dot{V}O_2$ at rest in most subjects. Only subject C3 and D4 achieved a METs-value above 3.0, which is considered as exercising at moderate intensity. $\dot{V}O_2$ during robotic walking of subject C5 was nearly the same as the resting $\dot{V}O_2$.

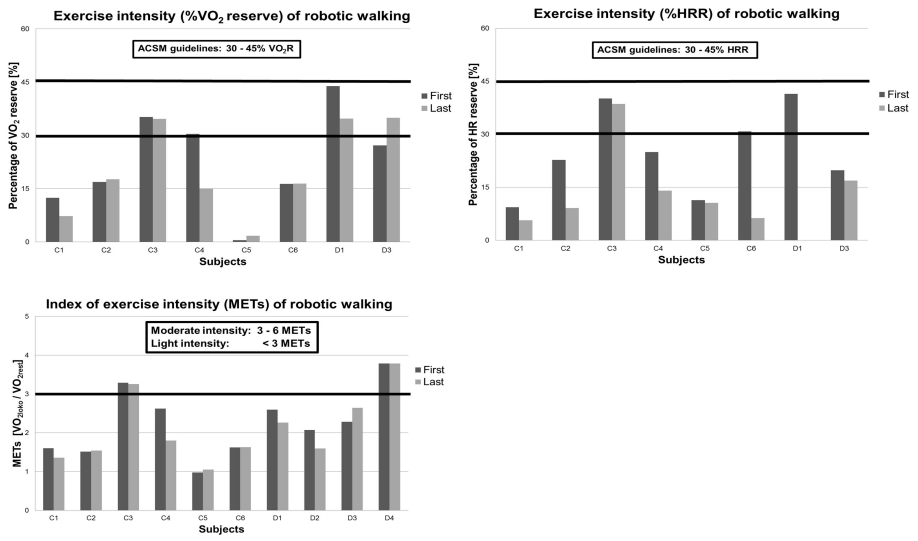

Figure 3. Individual values of %$\dot{V}O_2$R (upper-left), %HRR (upper-right) and METs (bottom-left) of robotic walking during both tested training sessions. The black lines indicate the recommended exercise intensity according to the ACSM guideline.[30] Most subjects exercised below this minimum level of exercise intensity. Dark bars indicate pretest, grey bars indicate posttest

DISCUSSION

In this study, exercise intensity of walking in the Lokomat was investigated in subjects with iSCI. Results indicate that the exercise intensity in these patients was predominantly below recommended levels for sedentary persons on both assessments during the study. Nevertheless, based on the submaximal $\dot{V}O_2$ and HR values during the arm crank test, this study shows that cardiorespiratory efficiency/fitness might have increased during the intervention. The fact that there was no change in peak $\dot{V}O_2$ of the arm exercise test does not necessarily suggest that cardiorespiratory fitness did not improve after the training program. Peak $\dot{V}O_2$ determined during an arm exercise test is mainly limited by local factors (small muscle mass) rather than central factors (lungs or heart).[32-34] Because the intervention was aimed at the legs, the exercise capacity of the arm muscle was assumed to be unchanged. Because of peripheral limitations, it is conceivable that the peak $\dot{V}O2$ as measured during an arm crank test did not change while subject's actual cardiorespiratory fitness did improve. Because of this limitation, we valued the submaximal values as more informative of whether cardiorespiratory fitness had improved. We used the arm crank test instead of a test using the lower limbs because we wanted to rule out the effect of possible improvements in neurological impairments in the legs elicited by the intervention. Such improvements would have the effect of an increased muscle mass being employed during the exercise test, which could lead to a higher $\dot{V}O_2$ that was not due to improvements in cardiorespiratory fitness. It appeared that after the robot-assisted gait training, subjects had a significantly lower submaximal heart rate during arm crank exercise at the same work load and $\dot{V}O_2$. Although this suggests improved cardiovascular efficiency, we did not find a significantly lower O_2 pulse. Furthermore, subjects had a significantly lower resting heart rate after a period of robot-assisted gait training, again suggesting an improved cardiorespiratory fitness. Although these results should be interpreted with caution, together these results indicate small improvements in cardiorespiratory fitness.

The improvements in cardiorespiratory fitness is rather surprising in light of the exercise intensity of the training program. The ACSM guidelines for exercise prescription,[31] and Ginis et al.[35] recommend that people with SCI should participate in an aerobic exercise activity of moderate to vigorous exercise intensity (30 - 60 %HRR or 30 – 60 %$\dot{V}O_2$R or 3.0 - 6.0 METs) at least twice per week. The majority of the subjects, however, did not reach this minimum level and exercised at very low intensity (<20% $\dot{V}O2$R or <20%HRR). In line with findings of the present study, Van den Berg et al.[36] found that a low-intensity training program (30% HRR) can improve physical capacity in untrained able-bodied subjects. Especially for sedentary people, low exercise intensity seems to be safer and is associated with a higher motivation.[37]

In this light, robotic walking may be an attractive low-intensity exercise mode for people with SCI.

Furthermore, the results showed that almost all subjects achieved lower submaximal $\dot{V}O_2$ and HR by performing the same robotic walking task after the training period suggesting an improved ability to employ the assistance of the device or an improvement in 'robotic walking economy'.[38] This improved ability to employ the assistance of the device or improvement in robotic walking economy might explain that most subjects had a lower %HRR at the end of the training program compared to the start. Furthermore, the average value of $\%\dot{V}O_2R$ was lower at the last training session suggesting that patients adapted to the training program. Although during every training session subjects were encouraged to contribute actively to the robotic walking activity, it was not always possible to reduce the robotic support in a way desirable, due to spasticity, risk of wounds and/or muscle weakness. This improved ability to employ the assistance of the device or improved walking economy was also observed in a study of the longitudinal changes in cardiopulmonary function during an intervention with robot-assisted gait training in two subjects with iSCI.[38] Nevertheless, contrary to our results, cardiorespiratory fitness did not improve in that study. The authors suggested that the improvement in robotic walking economy was mainly the result of a better gait pattern instead of changes in cardiopulmonary system.

The average level of exercise intensity of robotic walking found in this study (2.2 METs) was higher than found for passive walking in Jack et al.[24] (1.4 METs), but lower than for 'active' walking in studies of Israel et al.[23] and Hunt et al.[39](2.5 and 4.0 METs respectively). Israel et al.,[23] Hunt et al.[39] and Jack et al.[40] also presented values for peak $\dot{V}O_2$ (14, 16, 28 mL/kg/min, respectively) obtained during maximal active robotic walking that were substantially higher compared to values of the present study ($\dot{V}O_{2robot}$ = 6.8 mL/kg/min). During active walking in these studies, patients were supposed to push against the orthoses with their legs while walking. When walking with less guidance force applied to the legs, such an instruction would probably lead to emergency stops of the device since safety limits will be surpassed. Another explanation for the difference in exercise intensity between our study and literature is the level of impairment, given that the legs can be loaded more when less impaired. In the studies by Israel et al.,[23] Hunt et al.,[39] and Jack et al.[40] relatively more individuals with AIS D participated in the study than in our study. It is likely that the greater impairment of subjects in the present study has at least in part contributed to the lower exercise intensities found. Nevertheless, when subjects are encouraged to push against the orthoses of the Lokomat device during walking, as was done in Jack et al.,[40] it seems conceivable that exercise intensity can increase.

Limitations of this study are the small sample size and heterogeneity of the study

population, the latter resulting in interindividual differences in the level of physical capacity and the differences of exercise intensity of the intervention. Furthermore, the %$\dot{V}O_2$R and %HRR were calculated with the use of the resting and peak values of $\dot{V}O_2$ and HR. Resting $\dot{V}O_2$ was determined after five minutes of quiet sitting, which, although commonly used, might not be optimal when assessing resting values.[41] This might have resulted in overestimation of the resting values of $\dot{V}O_2$ and HR, which in turn results in underestimation of %$\dot{V}O_2$R and %HRR. On the other hand, the possibility exists that peak values of $\dot{V}O_2$ and HR were underestimated due to different factors such as subject's motivation, day-to-day variations, the exercise protocol and exercise modality. For this reason, the %HRR of the last assessment of subject D1 was excluded from the analyses. Furthermore, it was not possible to calculate valid values of %$\dot{V}O_2$R and %HRR in two subjects (D2 and D4), because they obtained their peak $\dot{V}O_2$ and HR during robotic walking instead of during the arm crank exercise test. An alternative would be that peak HR would be estimated based on age. However, this could result in overestimation of the maximal heart rate, since individuals with spinal cord injuries above the level of T4 may have impaired sympathetic innervations of the heart. Therefore, we chose the method presented in this paper. To complement the results of the %$\dot{V}O_2$R and %HRR we also calculated MET values. By comparing the $\dot{V}O_2$ and HR of both standardized robotic walking tasks, the assumption was made that external load was kept the same in both conditions. However, in this study the amount of hand rail support, which can influence the external load, was not completely standardized during both tests. Despite of this possible variation in external load, almost all subjects had a lower $\dot{V}O_2$ and HR at the last measurement compared to the first which still indicates an improvement in robotic walking economy.

Conclusion

The majority of the subjects exercised below the minimum level of the recommended exercise intensity (<30%$\dot{V}O_2$R/HRR and <3.0 METs). In spite of the low exercise intensity of the training program and no changes in peak $\dot{V}O_2$ of the arm exercise test, the lower resting and submaximal HR suggest that a period of robot-assisted gait training may have induced some improvement in cardiorespiratory fitness. However, because oxygen pulse did not show a significant improvement, likely improvements in cardiorespiratory fitness are small. Furthermore, almost all subjects had lower $\dot{V}O_2$ and HR during the same robotic walking task after the training period reflecting a higher robotic walking economy. Therefore, treadmill walking, including robot assisted walking, may not only help in improving walking ability, it might also have other secondary effects such as improvement in cardiorespiratory efficiency as found in this study. However, whether these effects are different from conventional therapy approaches may be studied in future randomized clinical trials.

REFERENCES

1. Buchholz AC, Pencharz PB. Energy expenditure in chronic spinal cord injury. Curr Opin Clin Nutr Metab Care. 2004 Nov;7(6):635-9.
2. Slentz CA, Houmard JA, Kraus WE. Exercise, abdominal obesity, skeletal muscle, and metabolic risk: evidence for a dose response. Obesity (Silver Spring). 2009 Dec;17 Suppl 3:S27-33.
3. Thijssen DH, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MT, Green DJ. Impact of inactivity and exercise on the vasculature in humans. Eur J Appl Physiol. 2010 Mar;108(5):845-75.
4. Haennel RG, Lemire F. Physical activity to prevent cardiovascular disease. How much is enough? Can Fam Physician. 2002 Jan;48:65-71.
5. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007 Aug;39(8):1423-34.
6. Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):247-57.
7. Alm M, Saraste H, Norrbrink C. Shoulder pain in persons with thoracic spinal cord injury: prevalence and characteristics. J Rehabil Med. 2008 Apr;40(4):277-83.
8. Dyson-Hudson TA, Kirshblum SC. Shoulder pain in chronic spinal cord injury, Part I: Epidemiology, etiology, and pathomechanics. J Spinal Cord Med. 2004;27(1):4-17.
9. Jain NB, Higgins LD, Katz JN, Garshick E. Association of shoulder pain with the use of mobility devices in persons with chronic spinal cord injury. PM R. 2010 Oct;2(10):896-900.
10. Davis GM, Hamzaid NA, Fornusek C. Cardiorespiratory, metabolic, and biomechanical responses during functional electrical stimulation leg exercise: health and fitness benefits. Artif Organs. 2008 Aug;32(8):625-9.
11. Hettinga DM, Andrews BJ. Oxygen consumption during functional electrical stimulation-assisted exercise in persons with spinal cord injury: implications for fitness and health. Sports Med. 2008;38(10):825-38.
12. van Asbeck FW, Post MW, Pangalila RF. An epidemiological description of spinal cord injuries in The Netherlands in 1994. Spinal Cord. 2000 Jul;38(7):420-4.
13. Hicks AL, Ginis KA. Treadmill training after spinal cord injury: it's not just about the walking. J Rehabil Res Dev. 2008;45(2):241-8.
14. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000 Nov-Dec;37(6):693-700.
15. Colombo G, Wirz M, Dietz V. Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord. 2001 May;39(5):252-5.
16. Alcobendas-Maestro M, Esclarin-Ruz A, Casado-Lopez RM, Munoz-Gonzalez A, Perez-Mateos G, Gonzalez-Valdizan E, Martin JL. Lokomat Robotic-Assisted Versus Overground Training Within 3 to 6 Months of Incomplete Spinal Cord Lesion: Randomized Controlled Trial. Neurorehabil Neural Repair. 2012 Jun 13.
17. Hornby TG, Campbell D, Zemon DH, Kahn JH. Clinical and Quantitative Evaluation of Robotic-Assisted Treadmill Walking to Retrain Ambulation After Spinal Cord Injury. Topics

in Spinal Cord Injury Rehabilitation,. 2005 Fall;11(2):1-17.
18. Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N, Hicks AL. Effects of body weight-supported treadmill training on heart rate variability and blood pressure variability in individuals with spinal cord injury. J Appl Physiol. 2005 Apr;98(4):1519-25.
19. Ditor DS, Macdonald MJ, Kamath MV, Bugaresti J, Adams M, McCartney N, Hicks AL. The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI. Spinal Cord. 2005 Nov;43(11):664-73.
20. Phillips SM, Stewart BG, Mahoney DJ, Hicks AL, McCartney N, Tang JE, Wilkinson SB, Armstrong D, Tarnopolsky MA. Body-weight-support treadmill training improves blood glucose regulation in persons with incomplete spinal cord injury. J Appl Physiol. 2004 Aug;97(2):716-24.
21. Soyupek F, Savas S, Ozturk O, Ilgun E, Bircan A, Akkaya A. Effects of body weight supported treadmill training on cardiac and pulmonary functions in the patients with incomplete spinal cord injury. J Back Musculoskelet Rehabil. 2009;22(4):213-8.
22. Hidler J, Hamm LF, Lichy A, Groah SL. Automating activity-based interventions: the role of robotics. J Rehabil Res Dev. 2008;45(2):337-44.
23. Israel JF, Campbell DD, Kahn JH, Hornby TG. Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther. 2006 Nov;86(11):1466-78.
24. Jack LP, Purcell M, Allan DB, Hunt KJ. The metabolic cost of passive walking during robotics-assisted treadmill exercise. Technol Health Care. 2011;19(1):21-7.
25. Turiel M, Sitia S, Cicala S, Magagnin V, Bo I, Porta A, Caiani E, Ricci C, Licari V, De Gennaro Colonna V, Tomasoni L. Robotic treadmill training improves cardiovascular function in spinal cord injury patients. Int J Cardiol. 2011 Jun 16;149(3):323-9.
26. Cai LL, Fong AJ, Otoshi CK, Liang Y, Burdick JW, Roy RR, Edgerton VR. Implications of assist-as-needed robotic step training after a complete spinal cord injury on intrinsic strategies of motor learning. J Neurosci. 2006 Oct 11;26(41):10564-8.
27. Ziegler MD, Zhong H, Roy RR, Edgerton VR. Why variability facilitates spinal learning. J Neurosci. 2010 Aug 11;30(32):10720-6.
28. Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, Donovan W, Graves D, Jha A, Jones L, Mulcahey MJ, Krassioukov A. Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. J Spinal Cord Med. 2011 Nov;34(6):547-54.
29. Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. Neurorehabil Neural Repair. 2009 Mar-Apr;23(3):197-206.
30. JH, Boesveldt S, Elbertse E, Berendse HW. Method to measure autonomic control of cardiac function using time interval parameters from impedance cardiography. Physiol Meas. 2008 Jun;29(6):S383-91.
31. Thompson WR GN, Pescatello LS et al. . American College of Sports Medicine: ACSM's Guidelines for exercise testing and prescription Eight edition ed. Philadelphia: Wolters Kluwer - Lippincott Williams & Wilkins; 2009.
32. Hopman MT, Dueck C, Monroe M, Philips WT, Skinner JS. Limits to maximal performance in individuals with spinal cord injury. Int J Sports Med. 1998 Feb;19(2):98-103.
33. Magel JR, McArdle WD, Toner M, Delio DJ. Metabolic and cardiovascular adjustment to arm

training. J Appl Physiol. 1978 Jul;45(1):75-9.
34. Sawka MN, Foley ME, Pimental NA, Toner MM, Pandolf KB. Determination of maximal aerobic power during upper-body exercise. J Appl Physiol. 1983 Jan;54(1):113-7.
35. Ginis KA, Hicks AL, Latimer AE, Warburton DE, Bourne C, Ditor DS, Goodwin DL, Hayes KC, McCartney N, McIlraith A, Pomerleau P, Smith K, Stone JA, Wolfe DL. The development of evidence-informed physical activity guidelines for adults with spinal cord injury. Spinal Cord. 2011 Nov;49(11):1088-96.
36. van den Berg R, de Groot S, Swart KM, van der Woude LH. Physical capacity after 7 weeks of low-intensity wheelchair training. Disabil Rehabil. 2010;32(26):2244-52.
37. Haskell WL. J.B. Wolffe Memorial Lecture. Health consequences of physical activity: understanding and challenges regarding dose-response. Med Sci Sports Exerc. 1994 Jun;26(6):649-60.
38. Jack LP, Allan DB, Hunt KJ. Cardiopulmonary exercise testing during body weight supported treadmill exercise in incomplete spinal cord injury: a feasibility study. Technol Health Care. 2009;17(1):13-23.
39. Hunt KJ, Jack LP, Pennycott A, Perret C, Baumberger M, Kakebeeke TH. Control of work rate-driven exercise facilitates cardiopulmonary training and assessment during robot-assisted gait in incomplete spinal cord injury. Biomedical Signal Processing and Control. 2008;3(1):19-28.
40. Jack LP, Purcell M, Allan DB, Hunt KJ. Comparison of peak cardiopulmonary performance parameters during robotics-assisted treadmill exercise and arm crank ergometry in incomplete spinal cord injury. Technol Health Care. 2010;18(4-5):285-96.
41. Compher C, Frankenfield D, Keim N, Roth-Yousey L. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc. 2006 Jun;106(6):881-903.

Chapter 7

Recovery of walking ability using a robotic device in individuals with incomplete spinal cord injury

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ABSTRACT

Objective: To perform a pilot-study to investigate the effects of a moderately intensive program of locomotor training consisting of robot-assisted treadmill training using the Lokomat device combined with additional conventional therapy in patients with incomplete spinal cord injury (SCI).

Design: Repeated assessment of the same patients or single-case experimental A-B design

Setting: The inpatient and outpatient clinic of a rehabilitation centre in Amsterdam
Participants: Eighteen patients with motor or sensory incomplete SCI (7 patients <1 year, 13 patients >1 year post-injury)

Intervention: One hour of Lokomat therapy was administered for 24 sessions within a period of 4 months with additional 30 minutes of conventional therapy.

Outcome measures: Primary outcome measure was walking speed during 10-meter walk test. Other outcome measures were, Functional Ambulation Category (FAC), Timed Get up and go test (TUG), Walking Index for Spinal Cord Injury II (WISCI II), Hoffer Classification, Berg Balance Scale (BBS) and Rivermead Mobility Index (RMI).

Results: Walking speed was significantly ($p<.05$) higher (on average .08 m/s) after the intervention compared to before the intervention. RMI also significantly improved during the intervention. Furthermore, we found a trend towards improvement in TUG and BBS. Other outcome measures (FAC, WISCI II, Hoffer classification) did not significantly change. Although at group level results were significant, there was quite some variation in the amount of improvement among subjects.

Conclusion: Walking speed may improve by this intervention in some patients, however, in most patients, gains in walking ability are small.

INTRODUCTION

The improvement of walking ability is an important goal during inpatient rehabilitation as well as during outpatient rehabilitation because even small gains in ambulation can make a meaningful amelioration of a patient's daily life.[1] In the last decade, gait training on a treadmill has been automated using robotic devices such as the Lokomat, a commercially available device.[2] To date, there are only a limited number of studies that have investigated the effectiveness of Lokomat therapy. A few quasi- experimental studies have demonstrated improved walking ability after Lokomat therapy in individuals with acute or chronic, mostly incomplete spinal cord injury (iSCI).[3-5] However, the authors of the three randomized clinical trials (RCTs) concluded that Lokomat therapy was not more effective than control therapies.[6-8] While these studies were ongoing, the controllers of the robotic orthoses of the device were improved making it possible to only partially assist the legs of patients instead of the original 100% guidance of the legs. The available randomized clinical studies in literature evaluate the effectiveness of Lokomat therapy with fully prescribed gait pattern only which may be lower than expected with more sophisticated control of the assistance in the gait pattern.[9]

In the Netherlands, because of limitations in the health care reimbursement system, only a limited amount of therapy is feasible. In current practice, this means that physical therapy is only possible for a limited number of therapy sessions each week. We investigated a training program outpatients could perform without too much interference with their daily life, and which could also be used for inpatient treatment. Currently, there are no studies reporting results of a study with a moderate (< 3 sessions a week) frequency of Lokomat therapy. Moreover, it is suggested that Lokomat therapy may be more effective when used in combination with overground therapy.[10-13]

The goal of this pilot study was to investigate whether walking speed and other gait related outcome measures would improve during an intervention in which the Lokomat device is used with more sophisticated settings with moderate frequency and additional conventional therapy a convenience sample of patients with iSCI. We hypothesized that patients would significantly improve their walking ability during the intervention period.

METHODS

Patients were recruited from both the inpatient and outpatient clinic of a rehabilitation center in Amsterdam. Patients were asked to participate if they were older than 17 years, had stable blood pressure and had a motor or sensory incomplete lesion according to ASIA classification[14] as a result of traumatic or non-traumatic

lesions of the spinal cord. Additionally, some sensory function needed to be intact in the legs. Exclusion criteria were: medical complications such as arrhythmias and unstable cardiovascular problems; severe skeletal problems such as osteoarthritis or osteoporosis of the lower limbs. All procedures were approved by the local ethics committee and all subjects gave written or oral (n=1) informed consent before participation.

Design

Patients were treated on the Lokomat for a total of 24 sessions. The goal was to train patients twice a week, for 12 weeks. However, due to logistics-related problems or health-related complications, we were not able to train all patients twice a week. Nevertheless, we made sure that the 24 session were performed within 4 months. When needed, patients incidentally received 3 therapy sessions a week to meet this goal. All outcome measures were assessed before and after the intervention.

Intervention

The device used for robot-assisted treadmill training was the Lokomat. The design and control of the Lokomat has been reported previously.[2] In this study, the LokomatPro device (Hocoma, Switzerland) was used with the Levi bodyweight support system. Three settings were manipulated during this study: speed, amount of body weight support (BWS) and the amount of assistance of the robotic orthoses, Guidance Force (GF). Patients were instructed to actively follow the walking pattern of the device. The ultimate goal was to walk at high but still comfortable speed, with as little BWS and GF as possible for as many minutes possible within the therapy time. No attempt was made to monitor the forces of the interaction between the participant and the device. We used settings the patients were still able to walk with for about 20-45 minutes without fatiguing. The duration of the training sessions was 60 minutes, including preparation time. Lokomat therapy was part of the normal rehabilitation program. Patients were allowed to perform other gait related therapies or activities when possible. We allowed the additional practice of walking overground to allow the transfer of skills from the treadmill environment to ADL-activities.[1,7,15-17]

Outcome measures

Before start of the intervention, demographic data were collected and ASIA classification was assessed (including upper- and lower-extremity motor scores, UEMS and LEMS, respectively). Primary outcome measure was walking speed at the timed 10m walk test. When patients were not capable of walking over the full 10-m walkway, walking speed was set to zero for the data analysis. We characterized

baseline stepping ability before start of the intervention by assessing whether patients were able to make at least one step, when necessary with a walker or side bars, but without long leg splints. Secondary outcome measures were Functional Ambulation Categories (FAC),[18] Berg Balance Scale (BBS),[19] Rivermead Mobility Index (RMI),[20] Hoffer classification (HOF),[21] self-selected Walking Index for Spinal Cord Injury II (WISCI II),[18] and Timed get-up and go test (TUG).[22]

Data Analysis

To compare the difference between outcome measures before and after training, we analyzed both the non-parametric and the parametric outcome measures using a Wilcoxon signed rank test, because of the small sample size and the non-normality of the data. A $p<.05$ was considered statistically significant. Effect size was calculated using r.[23] All analyses were performed using PASW version 18.0. Spearman correlation was used to study the relationship between LEMS and initial- and change in walking speed. Parametric data are reported as means with standard deviation. Non-parametric data are reported as median and interquartile range (IQR).

RESULTS

We recruited 21 subjects to participate in the study. Of these 21 patients, three subjects were not able to complete the 24 training sessions within four months. One subject had an injury not related to the intervention. For two other patients, Lokomat therapy was discontinued because they had severe unilateral knee-extensor spasm while walking in the Lokomat. Demographic data of the 18 patients who completed the 24 therapy sessions are presented in Table 1. There was great variation among patients before start of the intervention in lesion level, time after SCI and functional ability. Three patients were classified as ASIA B, 8 patients as ASIA C and 7 patients as ASIA D (Table 1).

Table 1: Patient characteristics at start of the study

Patient	Sex	Age (yrs.)	Time after SCI (yrs.)	ASIA classification and lesion level	LEMS pre	UEMS pre
1	M	21	0.4	B (L3)	16	50
2	F	66	5.7	D (C1)	41	50
3	M	23	0.4	D (C6)	39	41
4	M	63	0.4	D (C5)	50	34
5	F	33	0.2	C (C5)	13	38
6	F	58	17.3	C (Th4)	10	50
7	M	35	0.9	C (Th5)	19	50
8	F	34	7.7	D (Th7)	31	50
9	F	31	11.5	C (Th9)	25	50
10	M	55	2.2	C (Th4)	6	50
11	M	57	0.6	B (C4)	0	0
12	F	40	0.6	C (C6)	15	23
13	M	51	9.0	C (L1)	11	50
14	F	43	34.5	C (Th8)	12	50
15	M	55	2.5	B (Th7)	0	50
16	M	63	5.1	D (C3)	44	20
17	M	66	6.0	D (Th10)	26	50
18	M	62	1.2	D (Th10)	40	50
Group descriptives		48 (15)*	2.4 (7.4)#		18 (29)#	50 (13)#

LEMS=Lower extremity motor score according to ASIA. UEMS=Upper extremity motor score according to ASIA. * Mean (SD), # Median (IQR)

Changes in outcome measures

The primary outcome measure walking speed was significantly higher after (median 0.15 m/s, IQR=0.60) than before the intervention (median 0.09 m/s ,IQR=0.37), z=-2.621, p<0.009, r=0.44 average improvement in walking speed was 0.08 m/s. Figure 1 shows the individual values for walking speed before and after intervention, with the dotted line indicating the minimal detectable change in walking speed (>0.05 m/s,[7]). This minimal detectable change of walking speed is the size of the change required to exceed measurement error.[24] Nine patients improved their walking speed beyond this minimal detectable change. Furthermore, 5 patients did not regain 10 meter walking ability after the intervention (Table 2). Initial walking speed was related to LEMS (r=.68, p=.002), whereas change in walking speed was not (r=.16, p=.53).

Individual data of the secondary outcome measures on function are shown in

Table 2. Four patients who were able to make at least one step were not able to cover the full 10 meters of the walkway before the intervention. One of these patients (nr 14) was not able to perform the 10m walk test on both occasions because of pain in the ankle joint; (Table 2). When we performed the analysis again with the patients with an ability to make at least one step having the same walking speed before and after the intervention, there was still a significant (p=0.047) improvement during the intervention period in walking speed.

The median changes in outcome and results of the statistical analyses of RMI, BBS, FAC, WISCI II and Hoffer classification are presented in Table 3. Besides the improvement in walking speed, there was a significant improvement in the RMI (5 patients improved). Furthermore, there was a trend in the improvement of the Berg Balance Scale (4 patients improved). The Functional Ambulation Category, WISCI II score and the Hoffer classification did not change significantly (3 patients improved in FAC and WISCI II scores and 2 in the Hoffer classification). The TUG test could only be performed by 6 patients at start of the study and by 9 patients after the intervention. Patient 1 did not perform TUG after the intervention because of fatigue. We used 'last one carried forward imputation' for the analysis. The analysis of the six patients with 2 measurements for TUG revealed a trend (p=0.08) (5 patients improved their TUG).

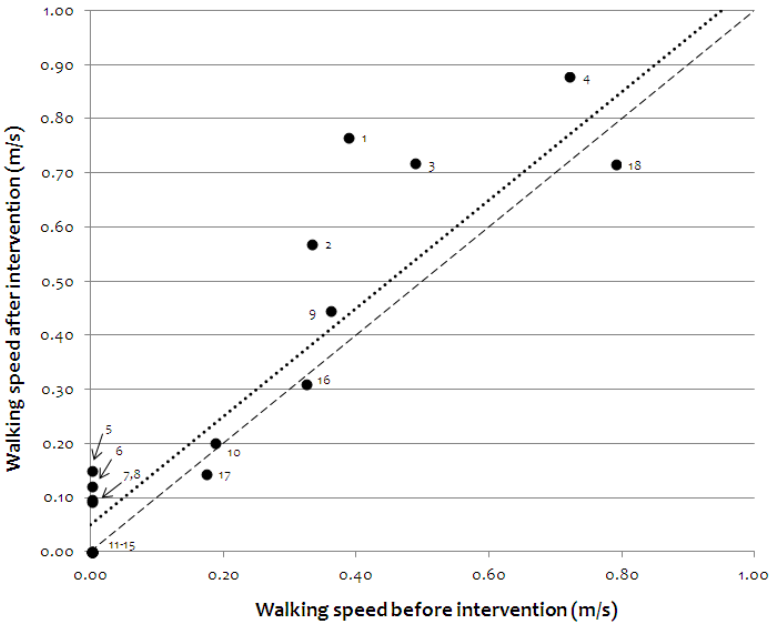

Figure 1: Individual results of walking speed measured before the intervention and after the intervention. The line of identity (x=y, dashed) and the line indicating clinically relevant improvement (x=y+0.05, dotted) is also depicted in the figure, along with labels of the individual patients.

Tabel 2: Functional abilities at start of the study and individual changes from start of the study to after the intervention

Patient	At least one step possible	Initial# walking speed (m/s)	Change in walking speed*	Initial RMI	Change in RMI*	Initial BBS	Change in BBS	Initial FAC	Change in FAC	Initial WISCI	Change in WISCI	Initial Hoffer	Change in Hoffer
1	Yes	0.39	0.38	5	4	14	0	4	1	9	0	2	1
2	Yes	0.33	0.24	9	0	15	0	4	0	13	0	2	0
3	Yes	0.49	0.23	11	0	42	1	4	0	9	0	3	0
4	Yes	0.72	0.16	13	0	51	3	5	0	13	7	4	0
5	No	0	0.15	2	4	4	2	0	2	0	13	2	0
6	Yes	0	0.12	6	2	11	0	2	0	8	0	2	0
7	Yes	0	0.10	6	4	14	8	3	1	12	1	2	1
8	Yes	0	0.09	7	1	22	0	4	0	13	0	3	0
9	Yes	0.36	0.09	7	0	13	0	4	0	7	0	2	0
10	Yes	0.19	0.02	5	0	13	0	2	0	6	0	1	0
11	No	0	0	0	0	0	0	0	0	0	0	1	0
12	No	0	0	2	0	2	0	0	0	0	0	1	0
13	No	0	0	5	0	17	0	0	0	9	0	1	0
14	Yes	0	0	6	0	14	0	4	0	12	0	2	0
15	No	0	0	5	0	8	0	0	0	0	0	1	0
16	Yes	0.32	-0.01	3	0	10	0	3	0	8	0	2	0
17	Yes	0.17	-0.03	7	0	13	0	4	0	13	0	2	0
18	Yes	0.79	-0.07	10	0	41	0	4	0	13	0	4	0

Initial = before start of the intervention. * Change is indicated as the outcome measured after the intervention – outcome measured before start of the intervention

Table 3: Changes in clinical test scores and corresponding P-values (Wilcoxon signed rank test)

	At start of intervention median (IQR)	After intervention median (IQR)	p-value	Change		Effect size (r)
				Median (IQR)	Average (SD)	
RMI (0-14)	6 (3)	7 (4)	0.04	0 (1.3)	+0.8 (1.5)	0.34
BBS (0-56)	14 (9)	13 (13)	0.07	0 (0)	+0.8 (2.0)	0.30
FAC (0-5)	3 (4.0)	4 (4)	0.10	0 (0)	+0.2 (0.6)	0.27
WISCI II (0-20)	9 (8)	9 (7)	0.11	0 (0)	+1.2 (3.4)	0.27
Hoffer(1-4)	2 (1)	2 (2)	0.16	0 (0)	+0.1 (0.3)	0.24

DISCUSSION

This pilot study showed that during an intervention of 24 sessions of Lokomat therapy combined with overground therapy walking ability can improve in patients with incomplete SCI. The primary outcome measure walking speed was not only significantly higher after intervention, average gain in walking speed exceeded measurement error (>.05m/s 7) and effect size was medium to large.[23] Furthermore, patients' bed mobility, postural transfers, and walking ability, as measured with the Rivermead Mobility Index, also improved significantly. Moreover, we found a trend for improved balance and there was an indication that performance of the timed-up and go test also improved. However, of the 9 patients who improved in walking speed beyond the minimal detectable change of 0.05 m/s,[7] it appears that 5 out of these 9 patients were within 1 year after onset of SCI. From literature, we know that spontaneous recovery is common in the first year after SCI.[25] It is therefore possible that the improvements of these patients are (at least partially) due to spontaneous recovery rather than to a therapy effect. On the other hand, the other 4 patients who improved in walking speed had a chronic lesion; for these patients we can assume that the improvements seen in these patients are due to therapy. Outcome measures focused on ambulatory status (Hoffer classification), independency of walking (FAC score), and amount of physical assistance, braces or devices (WISCI score) did not change significantly. Noteworthy is that, for the chronic group of patients, individual scores of WISCI, FAC, Hoffer and BBS tests did not change in our sample of patients. These results indicate that, for most patients, gains in walking ability were small. We, therefore, suggest that our intervention with moderate frequency may be effective for some patients, while it seems not effective for a number of patients.

In literature, lower extremity motor score (LEMS) has been assigned a role in explaining improvements in walking ability. The rate of recovery of LEMS is rapid during the first three months and the improvement plateaus between 9 months

up to 18 months.[25] LEMS measured shortly after SCI has been shown to predict the likelihood of independent walking one year after SCI.[26] In line with other studies, at baseline, we found that LEMS was significantly related to walking speed. In cross-sectional studies, a relation between LEMS and walking speed has been demonstrated for a group of patients with recent injury[27] and a group of ambulatory patients with chronic lesions.[28] However, in our study, change in walking speed was not related to initial LEMS, which is in line with a study in chronic patients, showing, that improvements in walking speed were not correlated with improvements in LEMS.[4] We did not measure LEMS after the intervention, so we cannot investigate whether changes in LEMS were related to changes in walking ability in this study.

Larger gains in outcome measures have been reported than in our present study, which might be due to differences in number of training sessions in the interventions studied. Most studies report effects of interventions that employed Lokomat therapy (or BWSTT) more than 2 sessions per week, even up to 5 times per week. The literature on the effectiveness of the Lokomat[4-8] is in line with the literature on studies on the effectiveness of BWSTT: in quasi experimental trials claimed positive effect for BWSTT,[1,29] while in an RCT (50+ patients per group) on the effectiveness of BWSTT[27,30] it was demonstrated that differences in improvement between BWSTT and overground therapy were not significant. Thus, currently there is no firm evidence suggesting that one therapy is more beneficial than others in improving walking ability after iSCI. Reviews stress the necessity of large scale RCTs to investigate the recovery of walking ability.[16,17,31]

Despite the minor changes in walking ability, there may be other rationales to prescribe Lokomat therapy for individuals with iSCI. Small gains in walking ability can make a difference for patient's lives.[1] It has been suggested that, even for patients who do not considerably improve walking ability, treadmill training may have benefits other than solely in the functional realm.[32] It is argued that BWSTT, and presumably robot-assisted therapy as well, have benefits associated with verticalization of the body, especially in wheelchair-dependent patients. In a randomized clinical study with non-ambulatory stroke subjects, for example, it was demonstrated that Lokomat therapy has the potential to improve body composition,[33] potentially decreasing cardiovascular risk factors. Furthermore, there are studies suggesting a potential for BWSTT to improve psychological well-being.[32] During interviews with the participants after the intervention in our study, subjects often indicated they had experienced beneficial effects not grasped by any of the measurement instruments used. Among those statements were 'My legs feel warm for more than a day after walking in the Lokomat, that's a pleasant feeling' (ASIA B), 'Now I can stand up straight, which makes dressing myself much easier' (ASIA C). 'Before the intervention I suffered from cystitis every 2 months. During the intervention period however, I have not had

urinary tract infection' (ASIA C) and 'I can defecate more easily (ASIA A, B). Although these statements are anecdotal, we believe they may provide indications for directions for future studies. Therefore, other secondary measurements should be performed to investigate the beneficial effects on other spectra of improvements of daily life than solely on the effectiveness of BWSTT or Lokomat therapy in improving walking ability.

To conclude, during our intervention with Lokomat therapy with additional overground walking, patients improve some aspects of walking ability. However, it is also important to note that a number of patients did not improve during the intervention which may have led, to unrealistic group results. This study does not confirm nor disprove the superiority of more loosely constraint limb trajectories as found in animal models. Future research should point out whether the Lokomat can perhaps be used more effectively, using different device settings, other volume or frequency of therapy, or in combination with other therapies. Before large scale multi centre trials are performed it is necessary to first identify the optimal use of the Lokomat, only then should larger efficacy trials be performed. Finally, since the costs of healthcare are rising, future studies should incorporate cost-effectiveness of this robot-assisted walking therapy.

REFERENCES

1. Harkema, S.J., Schmidt-Read, M., Lorenz, D., Edgerton, V.R., Behrman, A.L., Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training-Based Rehabilitation. Arch Phys Med Rehabil, 2011.
2. Colombo, G., Joerg, M., Schreier, R., Dietz, V., Treadmill training of paraplegic patients using a robotic orthosis. Journal of rehabilitation research and development, 2000. 37(6): p. 693-700.
3. Winchester, P., Smith, P., Foreman, N., Mosby, J.M., Pacheco, F., Querry, R., Tansey, K., A prediction model for determining over ground walking speed after locomotor training in persons with motor incomplete spinal cord injury. J Spinal Cord Med, 2009. 32(1): p. 63-71.
4. Wirz, M., Zemon, D.H., Rupp, R., Scheel, A., Colombo, G., Dietz, V., Hornby, T.G., Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil, 2005. 86(4): p. 672-80.
5. Schwartz, I., Sajina, A., Neeb, M., Fisher, I., Katz-Luerer, M., Meiner, Z., Locomotor training using a robotic device in patients with subacute spinal cord injury. Spinal Cord, 2011. 49(10): p. 1062-7.
6. Hornby, G.T., Campbell, D.D., Zemon, D.H., Kahn, J.H., Clinical and Quantitative Evaluation of Robotic-Assisted Treadmill Walking to Retrain Ambulation After Spinal Cord Injury. Topics in Spinal Cord Injury Rehabilitation, Fall/2005. 11(2): p. 1-17.
7. Field-Fote, E.C., Roach, K.E., Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther, 2011. 91(1): p. 48-60.
8. Alcobendas-Maestro, M., Esclarin-Ruz, A., Casado-Lopez, R.M., Munoz-Gonzalez, A., Perez-Mateos, G., Gonzalez-Valdizan, E., Martin, J.L., Lokomat Robotic-Assisted Versus Overground Training Within 3 to 6 Months of Incomplete Spinal Cord Lesion: Randomized Controlled Trial. Neurorehabil Neural Repair, 2012.
9. Israel, J.F., Campbell, D.D., Kahn, J.H., Hornby, T.G., Metabolic costs and muscle activity patterns during robotic- and therapist-assisted treadmill walking in individuals with incomplete spinal cord injury. Phys Ther, 2006. 86(11): p. 1466-78.
10. Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D.D., Kahn, J.H., Hornby, T.G., Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair, 2009. 23(1): p. 5-13.
11. Pohl, M., Werner, C., Holzgraefe, M., Kroczek, G., Mehrholz, J., Wingendorf, I., Hoolig, G., Koch, R., Hesse, S., Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil, 2007. 21(1): p. 17-27.
12. Dobkin, B.H., Duncan, P.W., Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair, 2012. 26(4): p. 308-17.
13. Dobkin, B.H., Progressive staging of pilot studies to improve phase III trials for motor interventions. Neurorehabil Neural Repair, 2009. 23(3): p. 197-206.
14. Maynard Jr, F.M., Bracken, M.B., Creasey, G., Ditunno Jr, J.F., Donovan, W.H., Ducker, T.B., Garber, S.L., Marino, R.J., Stover, S.L., Tator, C.H., International standards for neurological

and functional classification of spinal cord injury. American Spinal Injury Association. Spinal Cord, 1997. 35(5): p. 266.
15. Hicks, A.L., Treadmill training after spinal cord injury: It's not just about the walking. The Journal of Rehabilitation Research and Development, 2008. 45(2): p. 241-248.
16. Wessels, M., Lucas, C., Eriks, I., de Groot, S., Body weight-supported gait training for restoration of walking in people with an incomplete spinal cord injury: a systematic review. J Rehabil Med, 2010. 42(6): p. 513-9.
17. Swinnen, E., Duerinck, S., Baeyens, J.P., Meeusen, R., Kerckhofs, E., Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med, 2010. 42(6): p. 520-6.
18. Marino, R.J., Scivoletto, G., Patrick, M., Tamburella, F., Read, M.S., Burns, A.S., Hauck, W., Ditunno, J., Jr., Walking index for spinal cord injury version 2 (WISCI-II) with repeatability of the 10-m walk time: Inter- and intrarater reliabilities. Am J Phys Med Rehabil, 2010. 89(1): p. 7-15.
19. Berg, K., Measuring balance in the elderly: preliminary development of an instrument. Physiotherapy Canada, 1989. 41(6): p. 304-311.
20. Collen, F., Wade, D., Robb, G., Bradshaw, C., The Rivermead mobility index: a further development of the Rivermead motor assessment. Disability & Rehabilitation, 1991. 13(2): p. 50-54.
21. Hoffer, M., Feiwell, E., Perry, R., Perry, J., Bonnett, C., Functional ambulation in patients with myelomeningocele. The Journal of Bone and Joint Surgery (American), 1973. 55(1): p. 137-148.
22. Podsiadlo, D., Richardson, S., The timed" Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc, 1991. 39(2): p. 142.
23. Field, A., Discovering statistics using SPSS. 2009: Sage Publications Limited.
24. Tilson, J.K., Sullivan, K.J., Cen, S.Y., Rose, D.K., Koradia, C.H., Azen, S.P., Duncan, P.W., Meaningful gait speed improvement during the first 60 days poststroke: minimal clinically important difference. Phys Ther, 2010. 90(2): p. 196-208.
25. Fawcett, J.W., Curt, A., Steeves, J.D., Coleman, W.P., Tuszynski, M.H., Lammertse, D., Bartlett, P.F., Blight, A.R., Dietz, V., Ditunno, J., Dobkin, B.H., Havton, L.A., Ellaway, P.H., Fehlings, M.G., Privat, A., Grossman, R., Guest, J.D., Kleitman, N., Nakamura, M., Gaviria, M., Short, D., Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord, 2007. 45(3): p. 190-205.
26. Van Middendorp, J.J., Hosman, A.J., Donders, A.R., Pouw, M.H., Ditunno, J.F., Jr., Curt, A., Geurts, A.C., Van de Meent, H., A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. Lancet, 2011. 377(9770): p. 1004-10.
27. Dobkin, B., Barbeau, H., Deforge, D., Ditunno, J., Elashoff, R., Apple, D., Basso, M., Behrman, A., Harkema, S., Saulino, M., Scott, M., The evolution of walking-related outcomes over the first 12 weeks of rehabilitation for incomplete traumatic spinal cord injury: the multicenter randomized Spinal Cord Injury Locomotor Trial. Neurorehabil Neural Repair, 2007. 21(1): p. 25-35.
28. Kim, C.M., Eng, J.J., Whittaker, M.W., Level walking and ambulatory capacity in persons with incomplete spinal cord injury: relationship with muscle strength. Spinal Cord, 2004.

42(3): p. 156-62.
29. Wernig, A., Muller, S., Nanassy, A., Cagol, E., Laufband therapy based on 'rules of spinal locomotio' is effective in spinal cord injured persons. European Journal of Neuroscience, 1995 7: p. 823-829.
30. Dobkin, B., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., Ditunno, J., Dudley, G., Elashoff, R., Fugate, L., Harkema, S., Saulino, M., Scott, M., Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. Neurology, 2006. 66(4): p. 484-93.
31. Mehrholz, J., Kugler, J., Pohl, M., Locomotor training for walking after spinal cord injury. Cochrane Database Syst Rev, 2008(2): p. CD006676.
32. Hicks, A.L., Adams, M.M., Martin Ginis, K., Giangregorio, L., Latimer, A., Phillips, S.M., McCartney, N., Long-term body-weight-supported treadmill training and subsequent follow-up in persons with chronic SCI: effects on functional walking ability and measures of subjective well-being. Spinal Cord, 2005. 43(5): p. 291-8.
33. Husemann, B., Muller, F., Krewer, C., Heller, S., Koenig, E., Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 2007. 38(2): p. 349-54.

Discussion

The goal of this thesis was to evaluate the use of the Lokomat in rehabilitation practice after stroke and spinal cord injury. We studied the effectiveness of the device in improving walking ability, assessed the effects of walking in the device on the cardiorespiratory system, examined the muscle activity during walking in the device and studied the association between recovery of balance and recovery of strength of the paretic knee extensors. The first subsection of the discussion summarizes the main findings of this thesis and discusses a selection of methodological considerations in relation to the study design, selection of study populations and outcome measures. In the second subsection of this chapter, implications of present insights and recommendations for future research are discussed.

MAJOR FINDINGS AND METHODOLOGICAL CONSIDERATIONS

First, we'll discuss the choices we made for how we used the Lokomat and the frequency of the intervention. Next, the study on the evaluations of muscle activation during walking in the Lokomat will be discussed, whereupon the experiments on the evaluation of the effects of the Lokomat on the cardiorespiratory system are reviewed. Third, the effectiveness of improving walking ability using our intervention with the Lokomat are discussed. Finally, the evaluation of the relationship between balance and strength deficit after stroke is examined.

Considerations on the intervention and use of the device

Obviously, the Lokomat device can be employed in various ways, frequencies and durations. In the present thesis, the adjustments of the settings of the device were based on the clinical recommendations of the developer of the device (Hocoma, Switzerland), which in practice comes down to gradually decreasing the assistance of the device as much as possible. These recommendations are based on the opinion of a panel of expert researchers cooperating with the developer. In this thesis, the term 'optimal settings' refers to the settings with the assistance of the device decreased as much as possible while still allowing comfortable walking for the patients for a continuous bout of exercise.

The frequency and duration of the intervention was based on considerations of practical and financial feasibility. The Dutch reimbursement system and the organization in the rehabilitation centre allowed a certain amount of therapy per patient with stroke which limited the number of therapy sessions per week in the Lokomat to 2 sessions of one hour. Besides similar considerations for the choice of the frequency for the intervention of individuals with spinal cord injury, an additional feature of the intervention was that we did not want to intervene too much in the lives of the patients who had regular daytime jobs. All together, therefore, we think

that the frequency of the intervention is realistic in terms of what is presently possible within the present constraints of the daily life of patients and our health care system.

Muscle activity during walking in the Lokomat

Although walking in the Lokomat may be comfortable and may seem to generate near to normal kinematics of walking in even the most impaired patient, it is important to evaluate the (voluntary) activity during walking in the device to better understand possible mechanisms of therapy.[1] In chapter 2 we approached this by measuring muscle activity of several lower-limb muscles of individuals with stroke during walking both in the Lokomat device and during overground walking. The objective of this study was to compare walking in the Lokomat with minimal assistance as provided during regular therapy with walking overground. Detailed analyses of muscle activity revealed several differences during the gait cycle in the activity in various muscles. Apparently, muscle activity patterns (qualitatively) changed compared to the naturally occurring muscle activation patterns during overground walking. In order to produce a general statement on the effects of the support and restrictions of the device on muscle activity, we broke the stride up into two phases, stance phase and swing phase. The general picture is that during walking in the Lokomat, on average, the EMG amplitudes were equal or lower (although not always significantly) than during overground walking during both stance and swing phase. The significantly lower EMG amplitudes of the gastrocnemius muscle and the gluteus medius during stance phase of walking in the Lokomat may be caused by the assistance of the body weight support or the reduced degrees of freedom. The assistance of the orthoses during swing may have caused the decreased activity in the semitendinosus and tibialis anterior muscles. Although the activity of some muscles may be different during walking in the Lokomat compared to overground walking, this does not mean that it is not a suitable therapy to practice walking. Indeed, in severely affected neurological patients, degrees of freedom need to be reduced to make walking possible. Additionally, lower EMG suggests lower efforts of the muscles, which may allow patients to practice walking for longer duration.

A limitation of this study (chapter 2) may be the choice for the patients who were elected to participate in the experiment. The ability to walk independently was deemed important to be able to compare muscle activity patterns during overground walking with that during walking in the Lokomat. The participating patients had the same diagnosis as those recruited for the trial (chapter 4), but they had a much better walking ability. Another limitation may have been the limited experience the patients had with walking in the device. This appears to have led to sub-optimal settings (relatively high assistance) because, typically, more impaired patients enrolled in the trial (chapter 4) could already walk at more advanced settings after

a few training sessions. Together, therefore, the differences between robot-assisted walking and overground walking we observed in this study may not be indicative for more impaired individuals with experience in walking on the device and results should therefore be interpreted with caution. Furthermore, another limitation which should be controlled in future studies is the speed during Lokomat and overground walking. Speed has been demonstrated to affect muscle activity patterns during overground walking[2] and should therefore, preferably be similar during different modes of walking. However, in this regard, it is relevant to note that during walking in the Lokomat, horizontal propulsion of the centre of mass does not need to be generated by leg muscles, as the position of the pelvis and upper body is held over the same position of the treadmill by the device. This assistance of the Lokomat in the horizontal propulsion might affect the dependency of muscle activity during walking on speed. An indication that this may indeed occur is the finding of Hidler et al.[3] that EMG activity during walking in the Lokomat in healthy subjects did not change with different speeds. Nevertheless, it is possible that results of a similar future study will be different to ours if speed is controlled properly.

To answer more specific questions (such as temporal aspects of muscle patterns) of the effects of the restrictions and assistance of the device, more sophisticated statistical techniques are required (cross-correlations[4,5] or otherwise[1]). Future studies might address some of the concerns of physicians such as whether "patients can keep up with the speed of the device", or about the muscle activity of patients with ASIA B, or whether the paradigm of "forced use" can be applied during walking in the Lokomat. Finally, a systematic study of the effects of various combinations of assistance of the device at various speeds may be useful to determine optimal use of the device.

The effect of Lokomat training on the cardiorespiratory system

In chapter 3, we evaluated walking in the Lokomat in terms of the exercise intensity during walking in the device compared to walking overground. We were interested to learn what influence the restrictions and the assistance of the device had on the exercise intensity of patients. The results showed that exercise intensity levels during walking in the Lokomat in the group of stroke patients participating in this experiment were lower than during overground walking and 'light' according to general exercise recommendations. Based on these recommendations, Lokomat therapy would probably not lead to substantial improvements in cardiorespiratory fitness in stroke patients. Furthermore, in healthy subjects it was demonstrated that more challenging settings did not lead to higher cardiorespiratory intensities of walking. Therefore, we concluded that it is unlikely that substantial exercise intensity can be achieved in the Lokomat with the combination of settings used in

this experiment.

A limitation of this study (chaper 3) may be the use of healthy individuals as model for patients. It has been demonstrated that there are essential differences in exercise intensity during walking between hemiparetic stroke patients and healthy subjects.[6,7] Nevertheless, the most interesting part in the analysis of difference between patients and healthy subjects during different modes of walking is the observation of an interaction between mode of walking and subject group. It shows that patients respond differently to the assistance of the device than non-disabled subjects. Moreover, we did not find a significant difference between the exercise intensity during Lokomat walking in patients and healthy subjects, which may suggest that healthy subjects can be accepted as a model for patients for the purpose of this study. However, these analyses are limited by the heterogeneity of the patients in terms of walking ability and the differences in settings which were used during Lokomat walking among patients and between the group of patients and the group of healthy subjects. Therefore, because we cannot be sure whether healthy subjects are indeed valid models for patients we need to cautiously interpret the results that settings of the device did not affect exercise intensity found in healthy subjects. Moreover, whether our conclusion holds for other combinations of settings remains to be established.

In chapter 6 we studied the exercise intensity of walking in the Lokomat in patients with incomplete spinal cord injury. Similar to stroke patients, exercise intensity in this group of patients with spinal cord injury was 'light' compared to general exercise recommendations. Because Lokomat therapy may provide an alternative exercise modality for functional electrical stimulation-induced exercise in patients with a still intact sensory system, and for arm crank or wheelchair exercise for patients who may be prone to shoulder overuse, we studied the effects of a 24-session intervention with Lokomat training on cardiorespiratory fitness. As we were interested in improvements of cardiorespiratory fitness related to central adaptations rather than peripheral changes we performed an arm crank exercise test. We assumed that voluntary activation of the arms did not change during the course of the intervention. Although this may have been questionable for the two subacute patients (chapter 6, Table 1, Figure 2 C5, D2), inspection of the data showed that these patients did not improve in peak heart rate and peak oxygen consumption, indicating that it is unlikely that they employed more muscle mass during the pre-test. The results of the cardiorespiratory fitness test suggested that, despite the low exercise intensity, an improvement in cardiorespiratory fitness was realized. However, although the heart rate during rest and submaximal exercise decreased on average by 7 beats per minute, we did not find a significant increase in oxygen pulse. We therefore concluded that likely improvements were small.

This study is limited by not having a control group in the design. Whether there is a causal relationship between the intervention of Lokomat therapy with additional therapy can only be established in a controlled trial with a group of patients receiving similar amount of conventional therapy. Moreover, it should be noted that as patients also received additional therapy, the improvements of the cardiorespiratory fitness cannot be causally related to the therapy with the Lokomat alone. Therefore, our results should be interpreted with caution.

Recovery of walking ability using a robotic device after stroke

For people with stroke, we studied the effectiveness of improving walking ability using the Lokomat in a randomized clinical trial with 30 patients. Chapter 4 showed that the intervention we used in our study did not improve outcome after stroke significantly more than conventional overground physical therapy. Moreover, at follow-up measurements, there were no significant differences in improvements between groups in any of the outcome measures. Therefore, we concluded that the intervention we used in our study (8 weeks, 2 sessions/wk) was equally effective in improving walking ability as conventional therapy after stroke. We recommend that, for now, whether or not the present intervention with the Lokomat should be used in clinical practice should predominantly be based on cost-effectiveness or practical considerations for example on the number of available therapists to treat a patient with severely affected gait.

One of the qualities of this study is that it investigated an intervention that fitted both practically and financially in the organization of the rehabilitation centre and was only experimental in the sense of the content of the therapy, not in the amount of contact with physical therapists. Another quality of the study design is the relatively long follow-up period. Assessments at wk 24 and wk 36 after start of the study are rarely performed in the literature on the effectiveness of the Lokomat, but are essential to assess whether superiority of a therapy is permanent. Using such a design decreases the chance of a premature conclusion.

Limitations of the study were the different moments after stroke at which patients entered the study and the heterogeneity of impairment level of the patient group in combination with small sample size. This might raise concerns about the power of the analyses. However, the differences in improvements between control and intervention over the intervention period had low effect size for all outcome measures. Moreover, power analyses based on the available data revealed that 160 patients needed to be recruited to be able to demonstrate a significant improvement. As the effect size of such an analysis is small, the clinical relevance of such a result would be questionable.

Recovery of walking ability using a robotic device after spinal cord injury

Chapter 7 addressed the question of effectiveness of Lokomat therapy on improvements in walking ability and related outcomes after spinal cord injury. After the intervention period, patients significantly improvements in walking speed and Rivermead Mobility Index, indicating improved walking ability. Although results were significant at group level, it should be noted that there was quite some variation in the size of improvement among subjects. We used the minimal detectable difference for change in walking speed (0.05 m/s) to identify a 'true' improvement.[8] Researchers and clinicians can use this value to determine whether there is a true difference in performance or whether the difference between two tests is within measurement variability.[8] Results showed that 9 out of 18 patients improved beyond measurement variability. Moreover, to improve in outcome measures such as the Hoffer classification, the Functional Ambulation Categories and Walking index for Spinal Cord Injury, patients need to substantially improve in performance. The absence of significant improvements in these measures indicates that changes in walking ability are small. However, in line with Hicks et al.[9] we observed that Lokomat therapy might have value beyond the potential to improve walking ability. Through unstructured interviews, feedback was acquired on effects not measured by any of the outcome measures but which were beneficial for the patients (such as disappearance of urinary tract infections). Although these effects are anecdotal and not structurally studied, they may provide leads for new outcome measures for future research.

Because of the low prevalence of patients with incomplete spinal cord injury who were able to participate in a study in combination with the heterogeneity of the sample, we adopted a pre-experimental design without a control group. An alternative design might have been a cross-over design. However, if the condition under study can change rapidly regardless of the intervention, the use of this design is controversial.[10] Possibly, the strength of the evidence of this study could have been improved by performing multiple baseline measurements, that way, improvements due to 'latent capacity' could have been excluded.[11] The downside of more baseline measurements is that it conflicts with our goal of providing therapy as soon as possible.[12] The consequences of the use of our design is that it does not allow us to infer that the changes in walking ability were caused by our intervention or the Lokomat in particular, and results should therefore be interpreted with caution.[11]

Associations between strength of the paretic knee extensors and balance after stroke

In chapter 5 we demonstrated that absolute values of balance (measured with Berg Balance Scale) and isometric strength of the paretic knee extensors are interrelated at multiple assessments after stroke. Moreover, the regression coefficient seemed

to be higher as recovery progressed. This is possibly due to the combination of two findings in the literature on recovery after stroke: the relationship between initial impairments and reductions in impairment and compensation strategies that allow patients to improve (on average) relatively more in performance of functional activities than in impairment. Furthermore, we demonstrated a significant relationship between the change in balance and the change in strength of the paretic knee extensors over the interval of wk1-wk10 of the study, indicating that improvements in strength are associated with changes in balance. However, over the interval of wk10-wk24, there was no significant relationship between the change in isometric strength and changes in balance. These results indicate that differential mechanisms may be responsible for the recovery of these two variables. Strength can increase through improved voluntary activation or through increased cross-sectional area of the muscle. Possibly, during the interval of wk1-wk10, the improvements in strength were mostly due to improvements in voluntary activation, whereas during the interval of wk10-wk24, the improvements in strength were related to improvements in cross-sectional area of the knee extensors.[13] It is conceivable that improvements in strength due to improved voluntary activation are differently associated with improvements of balance compared to improvements in strength due to increased cross-sectional area. Alternatively, it is possible that inter-individual differences in improvements of balance, possibly through learning different compensatory strategies to maintain balance, have led to the non-significant relationship. Finally, other mechanisms, important for maintaining balance such as improved sensory integration or improved motor function in other muscles may have led to more variability in improvements in balance.

There are some methodological considerations of our study that need to be discussed. As a measure for balance we used the Berg Balance Score, which is suggested to be a measure of 'standing balance'[14] and which is often used in research and clinical practice and has good reproducibility.[15] Obviously, there are more ways to measure the concept of 'balance',[16] which might possibly lead to different insights. The measure we used for strength of the paretic leg (voluntary strength of the knee extensors) has some limitations. First, other muscles might be differently affected.[17] Second, in this study we could not differentiate between hypertrophy and improvements in voluntary activation. Third, the non-paretic voluntary activation is also affected after stroke, which we did not take into account.[17] Fourth, the relationships may be different when strength is measured at different knee angles and other joints.[18] Finally, isometric strength is not the same as dynamic strength or strength during synergistic movements.[19] These limitations should be kept in mind when interpreting the results.

Future studies may focus on the associations between the improvements

in performance of functional activities and improvements of variables at the impairment level, such as sensory function, and motor function of several muscles which should not be limited to the paretic side of the body. Such analyses are useful in understanding the relationship between changes in impairments and performance of functional activities. However, whether the associations found in our study change with statistical significance needs to confirmed using longitudinal statistics. In future studies, Generalized Estimating Equations or Random Coefficient Analyses can be used to test whether associations are significantly different. As we had only 23 subjects available for the analyses, we did not perform such an analysis as the analyses would be underpowered.

PRESENT INSIGHTS AND FUTURE STUDIES

Cochrane reviews and other systematic studies on effectiveness of therapy focused on improving walking ability after stroke conclude that there does not seem to be a clearly superior therapy available and that there is insufficient evidence to base firm conclusions on whether a certain therapy is superior in the long run.[20-24] Although two studies on the effectiveness of the Lokomat showed differentiating effects in improvements of walking ability with sub-acute stroke patients,[25,26] other studies did not find evidence for a superiority of any therapy.[27-29] Our results (chapter 4) add to the evidence suggesting that there is no difference between effectiveness of Lokomat therapy and conventional therapy on improving walking ability after stroke.

The literature on research on the effectiveness of therapy to improve walking ability after SCI is less abundant than for stroke. Presently there is debate on whether bodyweight supported treadmill training or Lokomat therapy should be used in rehabilitation after incomplete SCI.[30-33] The few RCTs performed suggest similar effectiveness compared to overground therapy.[34-38] Moreover, other studies, including systematic reviews, suggest that patients improve, regardless of therapy and that there is no evidence suggesting that any therapy is superior to another.[39-41] Unfortunately, our results (chapter 7) do not add strong evidence for effectiveness of Lokomat therapy, as we do not know whether improvements could have been realized with other therapies.

Taking the entire literature on functional recovery into account, some authors question whether therapy in rehabilitation practice is presently optimal and whether we are making any relevant contribution to recovery whatsoever.[42] In the following part of the discussion, implications of the present insights in neurorehabilitation and recommendations for future research are discussed. First, evidence for the potential for functional recovery in animals and humans is discussed. Second, future developments are touched upon and future research is suggested.

Functional recovery

Studies both on animals and humans suggest that functional recovery after neurological injury goes hand in hand with plastic changes in the structure of the brain (after stroke) or in the spinal cord (after SCI). Plasticity is broadly defined as the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections.[43] These changes in the central nervous system and concomitant functional improvements seem partly spontaneous (meaning not under our control or influence) and partly treatment induced.[44] The spontaneous recovery after stroke is associated with recovery of functionally inactive but viable tissue in the brain.[45] Treatment induced plasticity after lesions to the brain has been demonstrated in several studies by structural changes in the brain which could be explained by practice of the involved limb.[44,46] Early practice after brain lesion has effects on the size of projection areas of the brain after injury.[47,48] After spinal cord injury, spontaneous recovery is associated with sprouting or reorganization in the spinal cord unrelated to treatment.[49] Moreover, in SCI, there are indications that practice elicits changes at the spinal level.[50] Therefore, early rehabilitation practice is focused on bringing about changes in neural structure.[42,50]

Although animal studies have shown encouraging results, we need to be aware of essential differences in the recovery after brain injury between animals and humans and differences between study procedures. There seem to be crucial differences in the anatomy, and type of lesion between animal models for stroke and spinal cord injury and humans with stroke or spinal cord injury.[51] Furthermore, current intervention studies or therapies do not have similar doses of practice as animal studies nor similar levels of enrichment of the environment.[52,53] Nevertheless, these animal studies can provide a direction for studies in humans.

In humans, after stroke or SCI, it is presently not clear how much of the recovery is spontaneous and how much is treatment induced.[54] Indeed, for now, the equivalence of therapies may suggest that spontaneous recovery may be responsible for the larger part of improvements rather than any practice. Alternatively, it could suggest that both control and other interventions are (near) optimal therapies. The promising results of functional improvements by practice achieved in animal models, have not been replicated in humans.[42] According to theory, treatment induced improvements can be obtained through learning mechanisms.[55] Research on motor learning has produced several insights on how skills are acquired and which factors may lead to optimal learning.[56] The standard ingredients of motor learning are high-intensity, repetitive and task-specific practice. Furthermore, feedback on performance, goal setting, context specificity of therapy, patient motivation or engagement and specific instructions are related to more improvement.[56] Recently, in addition to these factors, the role of variability has been suggested as an additional rule in 'differential

learning'.[56,57] Some of these ingredients, intensity of practice and task specificity of practice, have already been demonstrated to result in enhanced functional recovery after stroke.[58,59]

Thus, through motor learning patients may be able to improve in function. Improvements in function are realized through the recovery mechanisms 'restitution' and 'compensation'.[60] Restitution leads to a return of the pre lesion movement, function, or tissue, whereas compensation is associated with emergence of new movement strategies that differ from the original, other functionality of neural tissue or compensatory use of other limbs.[60] Presently, there is still a lack of understanding of how much of functional recovery is achieved through restitution or compensation.[45] Efforts are made to come up with tests to elucidate the relative contribution to functional improvement.[61,62] Such information is valuable for clinical practice because it may help to optimize recovery.

In conclusion, animal studies and studies on changes in the central nervous system suggest that there may be some windows of opportunity to improve functional ability.[42] One major objective lying ahead of us is to identify an effective application of motor learning theory in an optimal intervention and to improve our understanding of why such an intervention is succesful.[55,56] For now, however, we can conclude that there is still a gap between what we think the potential for recovery is after stroke and spinal cord injury and what we have accomplished so far by interventions.

Future prospects for Lokomat and other robot-assisted therapies

Manufacturers of rehabilitation equipment have developed and continued to redesign products that may be used in research laboratories and in clinical practice. Besides the Lokomat, examples of such devices are the Lopes[63] or the Gait Trainer.[64] In the current healthcare market, these innovative devices create a demand for themselves in local rehabilitation centers and clinical administrators are purchasing such devices, and clinicians are implementing their use in rehabilitation practice before efficacy has been demonstrated. Because these innovations are becoming available on the market before efficacy has been properly demonstrated we need to treat such therapies as experimental therapies and may need to be cautious with implementing them in practice. Nevertheless, innovation in neurorehabilitation is needed and should be encouraged as current therapy outcome is not satisfactory. Moreover, these developments create chances for researchers as more funding may become available for these innovative therapies. The development of new therapies needs to go through a progressive staging of rigorous testing. The first step is to study how to optimally employ the devices in terms of adjusting settings such as speed, amount of body weight support, duration, intensity of training exercise.[11] Moreover, subgroups of patients for who this therapy is effective need to be

identified. Collaboration among several rehabilitation institutes is essential to gather such devices, particularly in a small country as the Netherlands.

We recommend that future studies on the effectiveness of therapy should include long term follow up assessments. There is convincing evidence that patients are capable of improving their performance of functional activities up to at least 1 year post stroke[65] and after SCI.[49] The importance of a follow-up measurement became particularly evident in a high quality trial (>400 participants) by Duncan et al.[66] which included follow-up assessments at 1 year after stroke. It was demonstrated that at 6 months there seemed to be a superior effect for one of the intervention groups. However, 1 year after stroke, all patients had improved relative to 6 months before and the group differences had disappeared. Such a result stresses the importance of long term follow-up measurements, since otherwise this can lead to an erroneous premature conclusion. The collected efforts to investigate the effectiveness of such device should therefore definitely include such long term follow-up measurements.

Some authors have suggested that early practice may lead to superior outcome.[67] If this proves to be true this will have drastic consequences for the organization of rehabilitation in the institutes in the chain of care. Moreover, increasing the frequency of repetitions and the 'volume' of therapy[42] will be an additional challenge when we want to apply it in the daily practice of rehabilitation of patients since there are many more problems that need attention during rehabilitation than only the rehabilitation of motor function. Nevertheless, robotic systems may have a role in these future developments because they have the potential to administer motor learning principles such as massed practice and (arguably) task specific and variable training especially for the severely impaired patients. Treadmill exercise, with or without a robotic device, that enables aerobic exercise could offer potential advantages for subgroups of more severely disabled persons. Moreover, further into the future, new treatments approaches will be tested and possibly implemented in routine rehabilitation such as brain stimulation in stroke (direct current stimulation[68] or transcranial magnetic stimulation[69]) or administering pharmaceuticals (such as Fluoxetine[70]). Examples for new treatments in development for SCI are (epidural) electrical stimulation techniques and pharmaceutical substances.[71,72] In the future, a combination of these treatments is possibly a sensible path to follow in neurorehabilitation. Meanwhile, we need to better understand recovery mechanisms and to try to apply this knowledge for optimization of therapy. One of the major challenges in neurorehabilitation research is to come up with a therapy and to indisputably demonstrate that we can permanently induce neurological and functional improvement in patients beyond the outcome of presently used therapies.

REFERENCES

1. Ricamato, A.L., Hidler, J.M., Quantification of the dynamic properties of EMG patterns during gait. Journal of Electromyography and Kinesiology, 2005. 15(4): p. 384-392.
2. Hof, A.L., Elzinga, H., Grimmius, W., Halbertsma, J.P.K., Speed dependence of averaged EMG profiles in walking. Gait Posture, 2002. 16(1): p. 78-86.
3. Hidler, J.M., Wall, A.E., Alterations in muscle activation patterns during robotic-assisted walking. Clin Biomech (Bristol, Avon), 2005. 20(2): p. 184-93.
4. Nelson-Wong, E., Howarth, S., Winter, D.A., Callaghan, J.P., Application of autocorrelation and cross-correlation analyses in human movement and rehabilitation research. J Orthop Sports Phys Ther, 2009. 39(4): p. 287-95.
5. Wren, T.A., Do, K.P., Rethlefsen, S.A., Healy, B., Cross-correlation as a method for comparing dynamic electromyography signals during gait. J Biomech, 2006. 39(14): p. 2714-8.
6. Waters, R.L., Mulroy, S., The energy expenditure of normal and pathologic gait. Gait Posture, 1999. 9(3): p. 207-31.
7. Zamparo, P., Francescato, M.P., De Luca, G., Lovati, L., di Prampero, P.E., The energy cost of level walking in patients with hemiplegia. Scand J Med Sci Sports, 1995. 5(6): p. 348-52.
8. Perera, S., Mody, S.H., Woodman, R.C., Studenski, S.A., Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc, 2006. 54(5): p. 743-9.
9. Hicks, A.L., Treadmill training after spinal cord injury: It's not just about the walking. The Journal of Rehabilitation Research and Development, 2008. 45(2): p. 241-248.
10. Mills, E.J., Chan, A.-W., Wu, P., Vail, A., Guyatt, G.H., Altman, D.G., Design, analysis, and presentation of crossover trials. Trials, 2009. 10(1): p. 27.
11. Dobkin, B.H., Progressive staging of pilot studies to improve phase III trials for motor interventions. Neurorehabil Neural Repair, 2009. 23(3): p. 197-206.
12. Mehrholz, J., Kugler, J., Pohl, M., Locomotor training for walking after spinal cord injury. Cochrane Database Syst Rev, 2008(2): p. CD006676.
13. Patten, C., Lexell, J., Brown, H.E., Weakness and strength training in persons with poststroke hemiplegia: rationale, method, and efficacy. J Rehabil Res Dev, 2004. 41(3A): p. 293-312.
14. Van Nes, I.J., van Kessel, M.E., Schils, F., Fasotti, L., Geurts, A.C., Kwakkel, G., Is visuospatial hemineglect longitudinally associated with postural imbalance in the postacute phase of stroke? Neurorehabil Neural Repair, 2009. 23(8): p. 819-24.
15. Blum, L., Korner-Bitensky, N., Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review. Phys Ther, 2008. 88(5): p. 559-66.
16. Tyson, S., Connell, L., How to measure balance in clinical practice. A systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. Clinical Rehabilitation, 2009. 23(9): p. 824-840.
17. Horstman, A.M., Beltman, M.J., Gerrits, K.H., Koppe, P., Janssen, T.W., Elich, P., de Haan, A., Intrinsic muscle strength and voluntary activation of both lower limbs and functional performance after stroke. Clin Physiol Funct Imaging, 2008. 28(4): p. 251-61.
18. Horstman, A., Gerrits, K., Beltman, M., Janssen, T., Konijnenbelt, M., de Haan, A., Muscle function of knee extensors and flexors after stroke is selectively impaired at shorter muscle lengths. J Rehabil Med, 2009. 41(5): p. 317-21.

19. Pohl, P.S., Duncan, P., Perera, S., Long, J., Liu, W., Zhou, J., Kautz, S.A., Rate of isometric knee extension strength development and walking speed after stroke. Journal of rehabilitation research and development, 2002. 39(6): p. 651-658.
20. French, B., Thomas, L., Leathley, M., Sutton, C., McAdam, J., Forster, A., Langhorne, P., Price, C., Walker, A., Watkins, C., Does repetitive task training improve functional activity after stroke? A Cochrane systematic review and meta-analysis. J Rehabil Med, 2010. 42(1): p. 9-14.
21. Meek, C., Pollock, A., Potter, J., Langhorne, P., A systematic review of exercise trials post stroke. Clin Rehabil, 2003. 17(1): p. 6-13.
22. Mehrholz, J., Werner, C., Kugler, J., Pohl, M., Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev, 2007(4).
23. Moseley, A.M., Stark, A., Cameron, I.D., Pollock, A., Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev, 2005(4).
24. Pollock, A., Baer, G., Langhorne, P., Pomeroy, V., Physiotherapy treatment approaches for the recovery of postural control and lower limb function following stroke: a systematic review. Clin Rehabil, 2007. 21(5): p. 395-410.
25. Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D.D., Kahn, J.H., Hornby, T.G., Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair, 2009. 23(1): p. 5-13.
26. Schwartz I., S.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): p. 516-523.
27. Husemann, B., Muller, F., Krewer, C., Heller, S., Koenig, E., Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke, 2007. 38(2): p. 349-54.
28. Chang, W.H., Kim, M.S., Huh, J.P., Lee, P.K., Kim, Y.H., Effects of Robot-Assisted Gait Training on Cardiopulmonary Fitness in Subacute Stroke Patients: A Randomized Controlled Study. Neurorehabil Neural Repair, 2011.
29. Mayr, A., Kofler, M., Quirbach, E., Matzak, H., Frohlich, K., Saltuari, L., Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair, 2007. 21(4): p. 307-14.
30. Dobkin, B.H., Duncan, P.W., Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair, 2012. 26(4): p. 308-17.
31. Harvey, L., Wyndaele, J.J., Are we jumping too early with locomotor training programs. Spinal Cord 2011. 49(Sept 2011): p. 947.
32. Wernig, A., Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. Neurology, 2006. 67(10): p. 1900; author reply 1900.
33. Dobkin, B., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., Ditunno, J., Dudley, G., Elashoff, R., Fugate, L., Harkema, S., Saulino, M., Scott, M., Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. Neurology, 2006. 66(4): p. 484-93.
34. Field-Fote, E.C., Roach, K.E., Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther,

2011. 91(1): p. 48-60.
35. Alcobendas-Maestro, M., Esclarin-Ruz, A., Casado-Lopez, R.M., Munoz-Gonzalez, A., Perez-Mateos, G., Gonzalez-Valdizan, E., Martin, J.L., Lokomat Robotic-Assisted Versus Overground Training Within 3 to 6 Months of Incomplete Spinal Cord Lesion: Randomized Controlled Trial. Neurorehabil Neural Repair, 2012.
36. Hornby, G.T., Campbell, D.D., Zemon, D.H., Kahn, J.H., Clinical and Quantitative Evaluation of Robotic-Assisted Treadmill Walking to Retrain Ambulation After Spinal Cord Injury. Topics in Spinal Cord Injury Rehabilitation, Fall/2005. 11(2): p. 1-17.
37. Schwartz, I., Sajina, A., Neeb, M., Fisher, I., Katz-Luerer, M., Meiner, Z., Locomotor training using a robotic device in patients with subacute spinal cord injury. Spinal Cord, 2011. 49(10): p. 1062-7.
38. Wirz, M., Zemon, D.H., Rupp, R., Scheel, A., Colombo, G., Dietz, V., Hornby, T.G., Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. Arch Phys Med Rehabil, 2005. 86(4): p. 672-80.
39. Mehrholz, J., Kugler, J., Pohl, M., Locomotor training for walking after spinal cord injury. Spine (Phila Pa 1976), 2008. 33(21): p. E768-77.
40. Swinnen, E., Duerinck, S., Baeyens, J.P., Meeusen, R., Kerckhofs, E., Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med, 2010. 42(6): p. 520-6.
41. Wessels, M., Lucas, C., Eriks, I., de Groot, S., Body weight-supported gait training for restoration of walking in people with an incomplete spinal cord injury: a systematic review. J Rehabil Med, 2010. 42(6): p. 513-9.
42. Krakauer, J.W., Carmichael, S.T., Corbett, D., Wittenberg, G.F., Getting Neurorehabilitation Right What Can Be Learned From Animal Models? Neurorehabil Neural Repair, 2012. 26(8): p. 923-931.
43. Cramer, S.C., Sur, M., Dobkin, B.H., O'Brien, C., Sanger, T.D., Trojanowski, J.Q., Rumsey, J.M., Hicks, R., Cameron, J., Chen, D., Chen, W.G., Cohen, L.G., deCharms, C., Duffy, C.J., Eden, G.F., Fetz, E.E., Filart, R., Freund, M., Grant, S.J., Haber, S., Kalivas, P.W., Kolb, B., Kramer, A.F., Lynch, M., Mayberg, H.S., McQuillen, P.S., Nitkin, R., Pascual-Leone, A., Reuter-Lorenz, P., Schiff, N., Sharma, A., Shekim, L., Stryker, M., Sullivan, E.V., Vinogradov, S., Harnessing neuroplasticity for clinical applications. Brain, 2011. 134(Pt 6): p. 1591-609.
44. Warraich, Z., Kleim, J.A., Neural plasticity: the biological substrate for neurorehabilitation. PM&R, 2010. 2(12): p. S208-S219.
45. Kwakkel, G., Kollen, B.J., Wagenaar, R.C., Understanding the pattern of functional recovery after stroke facts and theories. Restorative Neurology and Neuroscience, 2004. 22: p. 281-299.
46. Nudo, R.J., Plautz, E.J., Frost, S.B., Role of adaptive plasticity in recovery of function after damage to motor cortex. Muscle Nerve, 2001. 24(8): p. 1000-1019.
47. Yang, Y.R., Wang, R.Y., Wang, P.S.G., Early and late treadmill training after focal brain ischemia in rats. Neuroscience letters, 2003. 339(2): p. 91-94.
48. Nudo, R., Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. Journal of Rehabilitation Medicine-Supplements, 2003(41): p. 7-10.
49. Fawcett, J.W., Curt, A., Steeves, J.D., Coleman, W.P., Tuszynski, M.H., Lammertse, D., Bartlett, P.F., Blight, A.R., Dietz, V., Ditunno, J., Dobkin, B.H., Havton, L.A., Ellaway, P.H.,

Fehlings, M.G., Privat, A., Grossman, R., Guest, J.D., Kleitman, N., Nakamura, M., Gaviria, M., Short, D., Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord, 2007. 45(3): p. 190-205.
50. Lynskey, J.V., Belanger, A., Jung, R., Activity-dependent plasticity in spinal cord injury. Journal of rehabilitation research and development, 2008. 45(2): p. 229.
51. Dietz, V., Curt, A., Neurological aspects of spinal-cord repair: promises and challenges. The Lancet Neurology, 2006. 5(8): p. 688-694.
52. Nithianantharajah, J., Hannan, A.J., Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nature Reviews Neuroscience, 2006. 7(9): p. 697-709.
53. Birkenmeier, R.L., Prager, E.M., Lang, C.E., Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. Neurorehabil Neural Repair, 2010. 24(7): p. 620-635.
54. Kwakkel, G., Kollen, B., Twisk, J., Impact of time on improvement of outcome after stroke. Stroke, 2006. 37(9): p. 2348-53.
55. Krakauwer, J., Motor learning its relevance to stroke recovery and neurorehabilitation. Current Opinion in Neurology, 2006. 19: p. 84-90.
56. Beek, P.J., Roerdink, M., Evolving insights into motor learning and their implications for neurorehabilitation, in Textbook of Neural Repair and Rehabilitation, Selzer, C., Cohen, Kwakkel, Miller, Editor. 2012 (In Press), Cambridge University Press.
57. Schollhorn, W., Beckmann, H., Davids, K.W., Exploiting system fluctuations. Differential training in physical prevention and rehabilitation programs for health and exercise. Medicina (Kaunas), 2010. 46(6): p. 365-373.
58. Veerbeek J.M., K.M., Ket J.C.F., Wegen, van E.E.H., Kwakkel, G, Effects of Augmented Exercise Therapy on Outcome of Gait and Gait-Related in the first 6 months after stroke. A meta-analysis. Stroke, 2011. 42: p. 3311-3315.
59. Van de Port, I.G., Wood-Dauphinee, S., Lindeman, E., Kwakkel, G., Effects of exercise training programs on walking competency after stroke: a systematic review. Am J Phys Med Rehabil, 2007. 86(11): p. 935-51.
60. Levin, M.F., Kleim, J.A., Wolf, S.L., What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair, 2009. 23(4): p. 313-9.
61. Kitago, T., Liang, J., Huang, V.S., Hayes, S., Simon, P., Tenteromano, L., Lazar, R.M., Marshall, R.S., Mazzoni, P., Lennihan, L., Improvement After Constraint-Induced Movement Therapy Recovery of Normal Motor Control or Task-Specific Compensation? Neurorehabil Neural Repair, 2012.
62. van Asseldonk, E.H.F., Buurke, J.H., Bloem, B.R., Renzenbrink, G.J., Nene, A.V., van der Helm, F.C.T., van der Kooij, H., Disentangling the contribution of the paretic and non-paretic ankle to balance control in stroke patients. Exp Neurol, 2006. 201(2): p. 441-451.
63. Veneman, J.F., Kruidhof, R., Hekman, E.E., Ekkelenkamp, R., Van Asseldonk, E.H., van der Kooij, H., Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. Neural Systems and Rehabilitation Engineering, IEEE Transactions on, 2007. 15(3): p. 379-386.
64. Hesse, S., Uhlenbrock, D., A mechanized gait trainer for restoration of gait. Journal of

rehabilitation research and development, 2000. 37(6): p. 701-708.
65. Page, S.J., Gater, D.R., Bach, Y.R.P., Reconsidering the motor recovery plateau in stroke rehabilitation. Arch Phys Med Rehabil, 2004. 85(8): p. 1377-81.
66. Duncan, P.W., Sullivan, K.J., Behrman, A.L., Azen, S.P., Wu, S.S., Nadeau, S.E., Dobkin, B.H., Rose, D.K., Tilson, J.K., Cen, S., Body-Weight–Supported Treadmill Rehabilitation after Stroke. The new England Journal of Medicine, 2011. 364(21): p. 2026-36.
67. Bernhardt, J., Very early mobilization following acute stroke: Controversies, the unknowns, and a way forward. Annals of Indian Academy of Neurology, 2008. 11(5): p. 88.
68. Reis, J., Fritsch, B., Modulation of motor performance and motor learning by transcranial direct current stimulation. Current Opinion in Neurology, 2011. 24(6): p. 590.
69. Corti, M., Patten, C., Triggs, W., Repetitive Transcranial Magnetic Stimulation of Motor Cortex after Stroke: A Focused Review. American Journal of Physical Medicine & Rehabilitation, 2012. 91(3): p. 254.
70. Chollet, F., Tardy, J., Albucher, J.F., Thalamas, C., Berard, E., Lamy, C., Bejot, Y., Deltour, S., Jaillard, A., Niclot, P., Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. The Lancet Neurology, 2011. 10(2): p. 123-130.
71. Zorner, B., Schwab, M.E., Anti-Nogo on the go: from animal models to a clinical trial. Ann N Y Acad Sci, 2010. 1198 Suppl 1: p. E22-34.
72. Edgerton, V.R., Roy, R.R., A new age for rehabilitation. Eur J Phys Rehabil Med, 2012. 48(1): p. 99-109.

Summary

The Lokomat is a device consisting of a treadmill, body weight support system and two robotic orthoses which can guide the legs of severely affected neurological patients during walking on the treadmill. The goal of this thesis was to evaluate the use of the Lokomat in rehabilitation after stroke and spinal cord injury. We studied the effectiveness of the Lokomat in improving walking ability (**chapter 4 & 7**), assessed the effects of walking in the Lokomat on the cardiorespiratory system (**chapter 3 & 6**), examined muscle activation patterns during walking in the Lokomat (**chapter 2**) and studied the association between recovery of strength of the paretic leg and balance (**chapter 5**). **Chapters 2 to 5** were focused on stroke patients, whereas **chapters 6 & 7** were focused on patients with spinal cord injury.

To evaluate the influence of the assistance of the Lokomat and the limited degrees of freedom in terms of muscle activity we compared electromyography of leg muscles in stroke patients during walking in the Lokomat and during overground walking (**chapter 2**). Furthermore, a set of 'normative' muscle activity patterns was assessed in healthy subjects walking unassisted. Results showed that, in most muscles, activity was equal or lower than during overground walking. Furthermore, for some muscles, activity seemed less associated with a pattern of muscle activity corresponding to that of healthy individuals walking overground. We concluded that training in the Lokomat may elicit lower muscle activity and changes in the naturally occurring muscle activation patterns during walking in some muscles. These results may be explained by the body weight support, by the assistance provided by the orthoses and by the limitations in degrees of freedom of the Lokomat.

In **chapter 3**, we studied the influence of the assistance of the Lokomat and the limited degrees of freedom during walking in the Lokomat on the cardiorespiratory system by comparing heart rate (HR) and oxygen consumption ($\dot{V}O_2$) during walking in the Lokomat and during overground walking. We concluded that exercise intensity levels during walking in the Lokomat were 'light' according to general exercise recommendations and lower compared to overground walking in the group of stroke patients participating in this experiment. These results suggest that, using this type of therapy, patients will probably not substantially improve in cardiorespiratory fitness. Furthermore, we demonstrated that more challenging settings of the Lokomat did not lead to higher cardiorespiratory intensities during walking in the Lokomat in healthy subjects. These results may suggest that it is unlikely that patients with stroke achieve substantial exercise intensity during walking in the Lokomat with the combination of settings used in this experiment.

In **chapter 4**, we studied the effectiveness of the Lokomat relative to conventional therapies in improving walking ability in non-ambulatory stroke subjects involved in inpatient rehabilitation. The patients in the intervention group received 8 weeks of Lokomat therapy twice a week, together with 3 times 30 minutes a week of

conventional overground therapy. A control group received conventional assisted overground therapy during a similar amount of time. Outcome of therapy was assessed at study entry, after the intervention, and at wk24 and wk36 after baseline assessment. Patients showed significant improvements in walking speed, function and mobility, and strength of the paretic leg relative to baseline values at all assessments, but we found no significant differences between Lokomat and conventional training in improvements in any of the variables at any time during the study. Moreover, effect sizes of the differences in the improvements over the intervention period between groups were small in all outcome measures. We therefore concluded that Lokomat training is as effective as conventional training for increasing walking ability in non-ambulatory stroke patients.

In **chapter 5**, we evaluated the association of balance and strength of the knee extensors at multiple assessments during the rehabilitation process after stroke. Balance and strength can both be clearly affected after stroke. In several cross-sectional studies, performance of functional activities and measures of strength of the paretic leg have been shown to be related. However, during the rehabilitation process, both improve, and we have poor understanding of the course of the association of balance and strength of the knee extensors during the rehabilitation process. We demonstrated that there is a positive and significant relationship between these variables at all assessments. We observed that the association between balance and strength seems to improve over time, which is possibly due to the combination of two findings in the literature on recovery after stroke: the relationship between initial impairments and reductions in impairment and, secondly, the presence of compensation strategies that allow patients to improve (on average) relatively more in performance of functional activities than in impairment. Moreover, we found a significant association between changes in balance and changes in strength of the knee extensors over the period of wk1-wk10 of the study (relatively early after stroke), whereas there was no significant association over the period of wk10-wk24 of the study (relatively late after stroke). These findings may suggest that improvements of performance of functional activities are more related to improvements in voluntary activation than to improvements in cross-sectional area of the muscle. Alternatively, inter-individual differences in improvements in balance or improvements in other impairments which may affect balance (such as sensory function) may explain our results.

Interventions to promote physical activity in the spinal cord injury population are becoming increasingly important since being physically active may improve general health. In **chapter 6**, we studied the effect of a period of robot-assisted gait training on cardiorespiratory fitness. The training program consisted of a total of 24 training sessions on the Lokomat with additional conventional therapy. To assess

the intensity of the training program, $\dot{V}O_2$ and HR were measured during training sessions. Cardiorespiratory fitness was assessed before and after the intervention in a graded arm crank exercise test. Results suggested that, participants exercised at 'light' intensity according to general exercise recommendations. Analyses of data of the exercise test however, showed that submaximal and resting HR was significantly lower after the intervention, with no significant changes in $\dot{V}O_2$ suggesting higher stroke volume. However, oxygen pulse did not significantly change. We concluded that in spite of the low exercise intensity of Lokomat therapy, this intervention may have a positive effect on cardiorespiratory fitness. However, likely improvements in cardiorespiratory fitness are small.

In **chapter 7**, we studied the effects of an intervention of 24 sessions of Lokomat therapy with additional overground walking over 4 months on ambulatory function, balance, participation and general health. Although at group level some results showed significant improvements between pre- and post test, there was quite some variation in the size of improvement among subjects. Moreover, the lack of an effect in all gait related outcome measured suggested that improvements were small. We concluded that during our intervention with Lokomat therapy with additional overground walking patients improve some aspects of walking ability, however, in most patients, gains in walking ability are small.

Finally, implications of present insights and recommendations for future research are discussed in **chapter 8**. Literature on animal studies and motor learning suggest that recovery of function after neurological injury is possible through practice. However, there is still a gap between the suggested potential for recovery after stroke and spinal cord injury and what we have accomplished so far by interventions. Research needs to focus on how to optimize therapy based on current knowledge. Moreover, it is essential to gain knowledge about how to optimally employ the Lokomat in terms of adjusting settings such as speed, amount of body weight support duration, amount and type of assistance of the orthoses and frequency of training before a final verdict can be made on the effectiveness of the Lokomat, or any such device. Research should also focus on identifying possible subgroups of patients who might benefit from this therapy. In order to succeed in this, particularly in a small country as the Netherlands, collaboration between several rehabilitation institutes in gathering such information is essential. Moreover, further into the future, new treatments will be developed, probably combining our present knowledge of motor learning with newly developed therapies (e.g. with brain or spinal cord stimulation or pharmacological substances). In these future developments, robotic systems may have an important role.

Samenvatting

De Lokomat is een apparaat dat bestaat uit een tredmolen, een harnas voor lichaamsgewichtondersteuning en twee robot armen die de benen van neurologische patiënten kunnen begeleiden tijdens het lopen op de tredmolen. Het doel van dit proefschrift was om het gebruik van de Lokomat tijdens de revalidatie na beroerte of dwarslaesie te evalueren. Daartoe is de effectiviteit van de Lokomat in het verbeteren van de loopvaardigheid bestudeerd (**hoofdstuk 4 & 7**), zijn de effecten op het cardiorespiratoire systeem tijdens het lopen in de Lokomat beoordeeld (**hoofdstuk 3 & 6**), is de spieractiviteit onderzocht tijdens lopen in het de Lokomat (**hoofdstuk 2**) en is de relatie tussen herstel van kracht van de paretische kniestrekkers en balans na beroerte bekeken (**hoofdstuk 5**). **Hoofdstuk 2 tot en met 5** richten zich op patiënten met beroerte en **hoofdstuk 6 en 7** richten zich op patiënten met dwarslaesie.

Om de invloed van de assistentie van de Lokomat en de verminderde vrijheidsgraden te evalueren op de spieractiviteit (elektromyografie) van beenspieren van patiënten na een beroerte hebben we de spieractiviteit tijdens lopen in de Lokomat vergeleken met de spieractiviteit tijdens normaal lopen (**hoofdstuk 2**). Bovendien werd de spieractiviteit in een groep gezonde proefpersonen vastgelegd tijdens normaal lopen. De resultaten lieten zien dat de activiteit in de meeste spieren, lager of gelijk was tijdens lopen in de Lokomat vergeleken met normaal lopen. Voor sommige spieren was er bovendien een patroon te zien dat niet correspondeerde met het patroon van gezonde personen die normaal liepen. We concludeerden dat Lokomat lopen een lagere spieractiviteit kan veroorzaken die mogelijk verklaard kan worden door de lichaamsgewichtondersteuning, de hulp van de orthosen of de verminderde vrijheidsgraden van de Lokomat.

In **hoofdstuk 3** hebben we de invloed bestudeerd van de hulp van de Lokomat en de verminderde vrijheidsgraden tijdens lopen in de Lokomat op het cardiorespiratoire systeem door het meten van de hartslag (HR) en de zuurstofopname ($\dot{V}O_2$) tijdens lopen in de Lokomat en tijdens normaal lopen. We concludeerden dat de inspanningsintensiteit tijdens lopen in de Lokomat 'licht' was volgens algemene aanbevelingen voor inspanningsintensiteit en lager dan normaal lopen. Deze resultaten suggereren dat dit de therapie waarschijnlijk geen grote verandering in de cardiorespiratoire fitheid zal veroorzaken. Bovendien hebben we gedemonstreerd dat andere combinaties van instellingen van de Lokomat niet leidden tot hogere cardiorespiratoire intensiteit in gezonde proefpersonen. Deze resultaten suggereren dat het onwaarschijnlijk is dat er een substantiële inspanningsintensiteit gerealiseerd kan worden bij patiënten met de combinaties van instellingen die we hebben onderzocht in dit experiment.

In **hoofdstuk 4** hebben we de effectiviteit van Lokomat therapie onderzocht in het verbeteren van de loopvaardigheid in niet-zelfstandig lopende patiënten tijdens de revalidatie na een beroerte. De patiënten in de interventiegroep kregen gedurende 8 weken 2 uur per week Lokomat training in combinatie met 3 keer 30

minuten conventionele therapie gericht op loopvaardigheid. De controlegroep kreeg gedurende evenveel uur alleen conventionele therapie gericht op het verbeteren van de loopvaardigheid. Bij start van de studie, direct na de interventieperiode en op 24 en 36 weken na de start van de studie werd de loopvaardigheid vastgelegd. Tijdens de revalidatie gingen patiënten significant vooruit in de loopsnelheid, op functie en mobiliteit en op kracht van het paretische been. Er werden echter geen significante verschillen gevonden in de verbetering van uitkomstwaarden tussen de interventiegroep en de controlegroep. Bovendien was de 'effect size' van de verschillen in vooruitgang direct na de interventieperiode voor alle uitkomstwaarden klein. Daarom concludeerden we dat Lokomat therapie net zo effectief is als conventionele therapie in het verbeteren van de loopvaardigheid bij patiënten na een beroerte.

In **hoofdstuk 5** hebben we de relaties tussen balans en kracht van de paretische kniestrekkers bestudeerd op verschillende momenten tijdens het revalidatieproces. Balans en kracht kunnen na een beroerte beiden duidelijk aangedaan zijn. In verschillende cross-sectionele studies is er aangetoond dat deze variabelen gerelateerd zijn aan elkaar. Echter, tijdens de revalidatie veranderen beiden, en we weten niet wat dit voor invloed heeft op de relatie op verschillende momenten. Uit de resultaten bleek een significante relatie tussen de absolute waarden op verschillende meetmomenten die sterker leek te worden over de tijd. Deze bevinding kan worden verklaard door de combinatie van een relatie tussen initiële aandoening en de verbetering in functie en, ten tweede, dat functionele vaardigheden kunnen verbeteren door compensatie strategieën. Bovendien vonden we een significante relatie tussen veranderingen in kracht van de paretische kniestrekkers en veranderingen in balans over het interval van wk1-wk10 van de studie (relatief vroeg na revalidatie), terwijl er geen significante relatie was tussen veranderscores voor het interval van wk10-wk24 van de studie (relatief laat na revalidatie). Deze resultaten kunnen mogelijk worden verklaard doordat verbeteringen in functionele vaardigheden mogelijk meer gerelateerd zijn aan verbeteringen in vrijwillige activatie dan aan verbeteringen in de grootte van de spier. Een andere verklaring is mogelijk dat er inter-individuele verschillen zijn in verbetering van balans of verbeteringen van bijvoorbeeld sensorische functie die de balans beïnvloeden.

Interventies gericht op het bevorderen van fysieke activiteit bij mensen met een dwarslaesie worden steeds belangrijker omdat fysieke activiteit de gezondheid kan bevorderen. Daarom hebben we in **hoofdstuk 6** de effecten van een periode van Lokomat training op de cardiorespiratoire fitheid bestudeerd. Het trainingsprogramma bestond uit 24 trainingen met de Lokomat in combinatie met conventionele therapie. Om de cardiorespiratoire intensiteit vast te leggen werd zuurstofopname en hartfrequentie gemeten tijdens training met de Lokomat.

Cardiorespiratoire fitheid werd gemeten voor de interventieperiode en na de interventieperiode tijdens een inspanningstest met een arm ergometer. Resultaten lieten zien dat de inspanningsintensiteit tijdens lopen in de Lokomat' licht' was volgens algemene aanbevelingen voor inspanningsintensiteit. De resultaten van de inspanningtest lieten echter een significant lagere submaximale- en rusthartslag zien na interventie terwijl er geen significante verschillen waren in zuurstofopname, wijzend op een hoger slagvolume. Echter de zuurstofpulse verbeterde niet significant. We concludeerden daarom dat ondanks de lichte intensiteit van Lokomat therapie, deze interventie een positief effect zou kunnen hebben op cardiorespiratoire fitheid. Echter de verbetering in cardiorespiratoire fitheid is waarschijnlijk klein.

In **hoofdstuk 7** hebben we de effecten bestudeerd van een interventie van 24 Lokomat trainingen met extra conventionele therapie gericht op het verbeteren van loopvaardigheid, verdeeld over maximaal 4 maanden. Alhoewel er op groepsniveau significante verbeteringen gevonden werden was er behoorlijk wat variatie in de grootte van de verbetering binnen de groep patiënten. Bovendien suggereert dat het uitblijven van een effect op alle uitkomstwaarden die gerelateerd zijn aan loopvaardigheid dat de verbeteringen klein waren. We concludeerden dat patiënten sommige aspecten van loopvaardigheid verbeteren tijdens de interventie met Lokomat therapy en extra conventionele therapie, maar de verbeteringen zijn in de meeste patienten klein.

Tot slot zijn de implicaties van recente inzichten bediscussieerd en worden er aanbevelingen voor toekomstig onderzoek gedaan in **hoofdstuk 8**. De literatuur over dierstudies en motorisch leren suggereren dat herstel van functionele vaardigheden na neurologisch letsel mogelijk is door oefening. Er is echter nog steeds een kloof tussen het veronderstelde mogelijke herstel na een beroerte en na dwarslaesie en wat we tot nu toe hebben bereikt met interventies. Onderzoek moet zich richten op het optimaliseren van therapie op basis van wat we nu weten. Bovendien is het essentieel om kennis te vergaren over hoe de Lokomat optimaal gebruik moet worden in termen van instellingen zoals de snelheid, hoeveelheid lichaamsgewichtsondersteuning, hoeveelheid en type hulp van de orthosen en de duur en frequentie van de trainingen, voordat er een definitief oordeel gegeven kan worden over de effectiviteit van de Lokomat of vergelijkbare apparaten. Onderzoek moet zich ook richten op het identificeren van eventuele subgroepen van patiënten die mogelijk profijt hebben van deze therapie. Om hierin te slagen is het essentieel dat verschillende revalidatie instituten gaan samenwerken om deze informatie te verzamelen. Verder in de toekomst zullen nieuwe behandelingen ontwikkeld worden die onze kennis over motorisch leren combineren met nieuwe therapieën (zoals brein of ruggenmerg stimulatie). In deze toekomstige ontwikkelingen is er mogelijk nog een belangrijke rol weggelegd voor robotische systemen.

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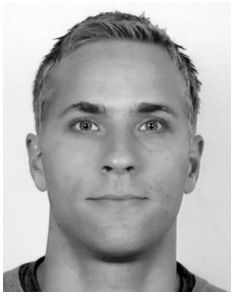
ABOUT THE AUTHOR



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