Recovery of gait after stroke

Boudewijn Kollen

Cover image: S. Zanen
Cover design: P.W. Gelderman

Revised edition

ISBN: 90 393 41 788

Printed by Ponsen & Looijen bv, Wageningen, The Netherlands

Recovery of gait after stroke

Herstel van loopvaardigheid na een beroerte

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr. W.H. Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op
dinsdag 14 maart 2006 des middags te 2.30 uur

door

Boudewijn Jozef Kollen
geboren op 26 februari 1954 te Amsterdam

Promotor: Prof. Dr. E. Lindeman
Department of Rehabilitation and Rudolf Magnus Institute of Neuroscience, University Medical Centre and Rehabilitation Centre De Hoogstraat, Utrecht

Copromotor: Dr. G. Kwakkel
Department of Rehabilitation and Rudolf Magnus Institute of Neuroscience, University Medical Centre and Rehabilitation Centre De Hoogstraat, Utrecht
Department of Rehabilitation, VU medical centre, Amsterdam

De totstandkoming van dit proefschrift werd mede mogelijk gemaakt door financiële steun van de Stichting Zwols Wetenschapsfonds Isala klinieken, het Van Leersumfonds KNAW en de Stichting Wetenschappelijk Fonds De Hoogstraat te Utrecht.

Aan Marjut, Jason en Krista

Contents

CHAPTER 1

Introduction

In the Netherlands annually about 30,000 people suffer a stroke for the first time.[1] One third of these stroke patients die within the first year, while 41% experience long term disabilities. This makes stroke a major disease in medical and in socio-economic terms. Based on the most recent family physician registrations available, the average incidence of stroke was estimated at 1.7 per 1,000 for men and 2.0 per 1,000 for women in 1994. However, the estimated average prevalence was much higher at 5.6 per 1,000 for men and 5.4 per 1,000 for woman.[2] Because stroke is mainly a disease of old age, the prevalence rate in individuals above 55 years of age is estimated at 25.2 per 1,000 for men and 27.7 per 1,000 for women. Incidence and prevalence rates have levelled off in recent years in the Netherlands.[3]
In the Netherlands stroke care consumes about 3 percent of the health care budget.[4,5] A large part of these costs is generated by home nursing services (16%), hospital care (20%), and nursing home care (37%).[4] Unfortunately, no prospective national data are available on the costs involved in stroke prevention, mental health care, and caregivers.

Not just on society but also, and far most, on the afflicted individual and his or her environment the impact is felt of a sustained stroke. For instance, a person's independence in moving about may be significantly compromised after stroke. Often patients are incapable of returning to their premorbidity roles in society or may even require long-term care. While stroke is the leading cause of long-term disability in the modern world, it is also a condition for which there is no universally accepted rehabilitation approach. Several impairment-focussed neurological treatment approaches have been developed and implemented in the 60s and 70s of last century but none were proven to be more effective than the other nor do these approaches generate functional improvements.[6] Recently developed treatment programmes that take advantage of compensation strategies with a strong emphasis on functional training may hold the key to optimal stroke rehabilitation.

The objective of stroke rehabilitation is to enable individual patients to achieve their full potential and to maximize the benefits from training in order to attain the highest possible degree of physical and psychological performance. Guidelines assist the clinician in this responsibility. The ultimate goals for many stroke patients are to achieve a level of functional independence necessary for returning home and to integrate as fully as possible into community life. For this reason clinicians are challenged at an early post-stroke stage to reliably predict the degree of disability the patient will ultimately experience in order to facilitate optimal stroke rehabilitation and appropriate discharge planning and implementation of resources.
Therapists and physicians need to formulate their functional goals as precisely as possible. These goals should be realistic depending on the levels of disability and potential for recovery. Overly optimistic expectations as well as underachievement must be avoided. This requires adequate knowledge of the patient and disease characteristics that determine functional outcome. Making a proper prognosis is far more complex than just applying a suitable prediction model. Ideally, this clinical decision making or clinical reasoning should be based on knowledge about recovery milestones.[7] The expected level of walking to a great extent determines the expected level of activities of daily living and possible discharge to home. However, each stroke patient is unique in its presentation of impairments (body functions and structures), disabilities and handicaps (limitation of activities and participation). The role of caregivers (environmental factor) could be crucial when planning for discharge destination.

Still a gap remains between prognostic research and rehabilitation practice, because only the results of relatively few well-designed prognostic studies are available for professionals to be integrated in stroke rehabilitation programmes. This affects the level of applied evidence based practice. Clinicians are largely dependent on the literature to satisfy their need for evidence based information. However, this information has usually limited clinical significance. This is because this evidence is often produced by cross-sectional studies that do not account for the non-linear nature of stroke recovery, which makes it difficult to validly

generalize this information in post-stroke time. For a valid interpretation of the non-linear nature and time-dependency of stroke recovery, information obtained from longitudinal conducted studies is required. Sequential repeated measurements in time will generate valuable information of recovery patterns, but studies that incorporate such longitudinal designs are often costly and laborious. However, if conducted properly, these studies gather valuable information about longitudinal relationships. In addition, longitudinal regression analysis makes it possible to study the impact of post-stroke time as time itself is considered one of the most important but neglected covariates in predicting stroke outcome.[8]
Since the late eighties of the last century, new statistical regression models for longitudinal analysis of repeated measurements have become available.[9] These methods can be used for the analysis of longitudinal relationships between body functions and limitation of activities and participation in time. The impact of time-dependent changes can also be established. These new methods are much more useful than the traditional MANOVA statistics. MANOVA for repeated measurements only takes into account subjects with complete data, ie the subjects who are measured at all time-points. MANOVA post-hoc procedures test the overall between-subjects group effect, ie only the difference between the average values of repeated measurements. Moreover, this method requires fixed time intervals.

To investigate the longitudinal relationship in recovery profiles of stroke patients, we used patient information from a previously conducted research project that involved a repeated measurement design with 18 measurements in the first year post stroke.[10] In that project statistical models for the prediction of activities of daily living after stroke were critically reviewed for methodological quality and the accuracy of therapists to predict functional outcome as well as the effects of different levels of augmented exercise training in stroke rehabilitation were studied.
In our project we focus almost primarily on the recovery of gait after stroke. For this purpose we use gait speed as the most important parameter to measure the

quality of gait recovery.[11] Reproducibility, validity and responsiveness are well documented for this measurement tool. The effects of post-stroke time, as a determinant for spontaneous recovery of gait, are largely unknown. By studying the course of recovery of gait in post-stroke time we attempt to contribute to this knowledge.

Objective and outline of this thesis

The objective of this thesis is to investigate the long term recovery of hemiplegic gait in severely affected stroke patients. In particular, the presence of a predictive relationship between early registered determinants and late outcome measures defined at 6 or 12 months, the relevance of longitudinally applied frequent measurements to establish such a relationship and the long term effects of intensity of stroke rehabilitation are investigated.
Because of the course of stroke recovery is non-linear and time-dependent, early and late recovery was studied. This required the establishment of acute, subacute and long term recovery profiles. This information subsequently assisted in the interpretation of the mechanisms involved in the long term recovery of hemiplegic gait and the impact of therapeutic interventions on this recovery. Based on multiple reproducible, valid and responsive measurement instruments, high quality clinimetric data was obtained longitudinally within the first post-stroke year. This information was than used to address the specific research questions in the projects complementing this thesis.

First, a review of current research developments is presented of functional recovery after stroke (chapter 2). This chapter is the starting point of this thesis and provides background information and an overall framework of issues relevant to subsequent chapters.
Thereafter, the relationship between comfortable and maximal walking speed during the first post-stroke year is explored and its relevance and therapeutic implications are discussed (chapter 3). Because little is known of the early characteristics of patients that may contribute to the restoration of walking

ability, stable predictive determinants of independent gait at 6 months post-stroke are studied (chapter 4). The selection of variables for this new model is based on significance in bivariate logistic regression each and every week during the entire initial 10 week post-stroke onset period. Subsequently, the effects of repeated measurements on an appraisal based walking classification over time are studied to determine time related effects (chapter 5). For this purpose the longitudinal relationship between comfortable walking speed and Functional Ambulation Categories (FAC) for independent gait is investigated between the fourth and twenty-sixth post-stroke weeks. The longitudinal relationship between functional change in walking ability and change in time-dependent covariates is explored during the first post-stroke year and a multivariate multi-level regression model for the prediction of longitudinal change in walking ability is developed (chapter 6). By modelling only change scores longitudinal rather than longitudinal and cross-sectional relationships are analyzed in the regression model.

New creative ideas based on clinical expertise and principles of motor learning are needed to advance the development of stroke rehabilitation programmes for the benefit of the large population of chronic stroke victims. Therefore, a single subject design was used to explore the possible benefits to stroke patients of a training regimen commonly used in competitive sports (chapter 7). The effects of overloading of the lower hemiparetic extremity on walking speed in chronic stroke patients were analysed. The long term impact of intensive rehabilitation programmes on functional recovery is a relevant issue to address because of the costs and resources involved to implement and maintain these programmes. In a randomized controlled trial the effects of these programmes in the acute and subacute rehabilitation phases are studied in patients at one year after stroke (chapter 8). Finally, a literature based review is presented of the facts and theories of the non-linear functional recovery patterns after stroke (chapter 9). The mechanisms that are presumed to be involved in this recovery are discussed.

For this research project patient information was obtained from two sources. First, the main studies of this thesis, described in chapters 3, 4, 5, 6 and 8, were based on information obtained from patients enrolled in another study project already published elsewhere.[10] For that project 102 stroke patients were used. These patients were recruited from seven hospitals in and around the Amsterdam area during a 32 months period from 1994 to 1997. Moreover, three rehabilitation centres and 15 nursing home facilities participated in the hospital based research project. The original project was coordinated by the Physical Therapy department of the Vrije Universiteit medical centre and approved by the ethics committee of each participating medical facility. In order to create a relatively homogeneous study population, patients were enrolled when they met the following admission criteria:

1. had suffered a primary ischemic stroke involving the middle cerebral artery (MCA) as revealed by CT- or MRI-scan,
2. were between 30 and 80 years old,
3. presented with an impaired upper and lower extremity motor function,
4. were unable to walk at first assessment,
5. had no complicating medical history, such as cardiac, pulmonary or other neurological disorders,
6. had no severe deficits in communication, memory and understanding,
7. provided informed consent.

Consequently, the statistical analyses of the main studies of this thesis were conducted on ample available patient information necessitating no acquisition of additional data for the present research project.
Reformulating research questions in such a way that these questions specifically address the non-linear nature and time-dependency of recovery of gait after stroke and reanalysing data from the original study project using statistical methods that correct for within-subject dependency required for analysis of longitudinal data are characteristic elements of this new project. The studies in this new project will generate results that will complement those of the original study project, but likewise will also raise new questions.

Second, from the patient records of the Department of Rehabilitation Medicine in the Isala klinieken in Zwolle three chronic stroke patients were selected with stage 3 or 4 Fugl-Meyer scores in the lower extremity and the ability to ambulate independently without walking aids for 5 minutes. Subsequently, these patients were invited to participate in the single subject design study described in chapter 7.

In the general discussion of this thesis an attempt is made to elaborate on the reported findings and to present an overall assessment of the scientific significance of the studies in this thesis as well as any suggestions for further research.

REFERENCES

1. Evers SMAA, Struijs JN, Ament AJHA, van Genugten MLL, Jager JC, van den Bos GAM. The disease impact, health care management, and costs of stroke in the Netherlands. RIVM report 282701001/2002.
2. Herman B, Leyten AC, van Luijk JH, Frenken CW, Op de Coul AA, Schulte BP. Epidemiology of stroke in Tilburg, the Netherlands. The population-based stroke incidence register: 2. Incidence, initial clinical picture and medical care, and three-week case fatality. Stroke 1982; 13: 629-34.
3. Rijksinsituut voor Volksgezondheid en Milieu (RIVM). Volksgezondheid Toekomst Verkenning. Maarssen: Elsevier/De Tijdstroom 1997.
4. Evers SM, Engel GL, Ament AJ. Cost of stroke in the Netherlands from a societal perspective. Stroke 1997; 28: 1375-81.
5. Evers SMAA, Goossens MEJB, Ament AJHA, Maarse JAM. Economic evaluation in stroke research: An introduction. Cerebrovascular diseases 2001; 11: 82-91.
6. Peppen van RPS, Kwakkel G, Wood-Dauphinee S, Hendriks HJM, Van der Wees PhJ, Dekker J. The impact of physical therapy on functional outcome after stroke: What’s the evidence? Clinical Rehabilitation 2004; 18: 833-862.
7. Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation - A critical review of the literature. Physiotherapy 1999; 85: 377-391.
8. Gresham GE. Stroke outcome research. Stroke. 1986; 17: 358-362.

9. Zeger SL, Liang K-Y. An overview of methods for the analysis of longitudinal data. Stat Med. 1992; 11: 1825–1839.
10. Kwakkel G. Dynamics in functional recovery after stroke. Ponsen & Looijen BV, The Netherlands. 1998.
11. Lamontagne A, Fung J. Faster is better. Implications for speed-intensive gait training after stroke. Stroke. 2004; 35: 2543-48.

CHAPTER 2

Functional recovery after stroke:
A review of current developments in stroke rehabilitation research

Boudewijn Kollen, Gert Kwakkel, and Eline Lindeman

Reviews on Recent Clinical Trials 2006; 1: 75-80

Abstract

This review article discusses current research developments in functional recovery after stroke. With the institutionalization of stroke services across health care facilities a reduction in mortality rates, length of inpatient stay and improved independence in activities of daily living have been reported. Several systematic reviews show that traditional treatment approaches induce improvements that are confined to impairment level only and do not generalize to a functional improvement level. More recently developed treatment strategies, that incorporate compensation strategies with a strong emphasis on functional training, may hold the key to optimal stroke rehabilitation. Intensity and task-specific exercise therapy are important components of such an approach. Guidelines may assist the clinician in this responsibility. However, due to marked heterogeneity of the stroke population and poor methodological quality of many studies results are uncertain. Several options are discussed to overcome the problem of stroke heterogeneity in research designs.

Longitudinal repeated measurements designs are required to study the effects of non-linearity and time dependency of functional recovery in stroke. Furthermore, prognostic research based on sound clinimetric data generates relevant information that may guide the clinician in clinical decision making and in determining optimal treatment strategies.

INTRODUCTION

Stroke is a disease of developed nations. Worldwide it is increasing along with modernization. In the United States (US) stroke is the third leading cause of death and leading cause of serious, long-term disability.[1] While stroke mortality rates have declined, the number of total stroke deaths has increased in the US in the 1990s. This trend may continue as the percentage of older individuals grows. It is estimated that there are over 750,000 first-ever or recurrent cases of stroke in the US each year.[2] Strokes occur at any age but are much more common in the elderly, with the death rate doubling every ten years between 55 and 85.[1] Both life expectancy and incidence of stroke is increasing in the United States.[3] It is anticipated that by 2020, stroke will have moved from the 6th leading cause of lost disability adjusted life years (DALY's) to 4th.[4] The expected increase in stroke survivors potentially living with disabilities will place a burden on the survivor's family, the community, and the healthcare system. Because of the substantial costs and their impact on society much attention is paid to the prevention of stroke. Major preventable risk factors include hypertension, atrial fibrillation, diabetes, and tobacco consumption as well as hypercholesterolemia and obesity. Moreover, a meta-analysis has demonstrated that moderate to high levels of physical activity are associated with reduced risk of total, ischemic, and hemorrhagic strokes.[5]

New developments in stroke treatment induced changes in stroke care and the necessity to concentrate this care in specialized, well organized and coordinated medical facilities, hence creating stroke services. The scientific evidence for the benefits of these stroke services is mounting. As a consequence many health care facilities and institutions proceeded to incorporate such a service. A stroke unit is part of a stroke service. At present stroke units can be found within a large number of hospitals. A reduction of mortality rates and length of inpatient stay and improved independence in activities of daily living (ADL) have been demonstrated for patients who are admitted to a stroke unit.[6-8] These benefits have been attributed to an integrated approach in which acute care is linked with early mobilization and rehabilitation as well as the prevention of post-stroke complications, comprehensive assessment of medical problems, impairments and disabilities, active physiological management, skilled nursing care, early setting of rehabilitation plans involving carers and early assessment and planning for discharge needs.[9-11] Stroke units employ a team of experts on stroke care. Such a team incorporates a neurologist, specialized registered nurses, physiatrist, physiotherapist, occupational therapist, speech pathologist, social worker, and a transfer nurse. In addition, a neuropsychologist, geriatrician, psychiatrist, dietician, cardiologist, internist, neurosurgeon and Ear, Nose and Throat physician may be consulted if required. In a systematic review Langhorne and Duncan showed that there can be substantial benefit from organized inpatient multidisciplinary rehabilitation in the postacute period.[12] Based on a heterogeneous group of 9 trials totalling 1,437 patients, they found a reduced odds of death (OR: 0.66 CI: 0.49 to 0.88; p = 0.01), death or institutionalization (OR: 0.70 CI: 0.56 to 0.88; p = 0.001), and death or dependency (OR: 0.65 CI: 0.50 to 0.85; p = 0.001), which was consistent across a variety of trial subgroups.

Based on this information the following questions with regard to stroke rehabilitation will be addressed:

1. Is stroke rehabilitation efficacious?
2. Is methodological quality of studies sufficient in stroke rehabilitation research?
3. What is the significance of repeated measurements for the prediction of stroke recovery?

EFFICACY OF STROKE REHABILITATION

The importance of evidence-based medicine and practice as a guide to the clinical decision-making process is increasingly recognized by health care professionals. In the absence of any curative therapy, rehabilitation constitutes the main mode of therapy to improve quality of life following stroke[13] and is considered a corner stone of multidisciplinary stroke care.[14] However, to date the choice of applied therapeutic interventions is still subject to empiricism and demonstration of their efficacy is often based on methodologically low quality research. One way of assessing the quality of randomized controlled trials (RCT) is with the Physiotherapy Evidence Database (PEDro) scale.[15] This rating allows for distinguishing between methodological sound and poor trails. This instrument has been used in a systemic review for determining the evidence for the impact of physical therapy on functional outcomes after stroke.[16] For this review, from the 735 publications identified as clinical trials in stroke rehabilitation, 151 studies were selected including 123 randomized controlled trials (RCT) and 28 controlled clinical trials (CCT). Methodological quality of all RCTs constituted 5 median points on a 10 point PEDro scale. The effects generated by different neurological treatment approaches, including Bobath or Neurodevelopmental treatment (NDT), Brunnstrom, Rood, Johnstone, Proprioceptive Neuromuscular Facilitation (PNF), Motor Relearning Programme (MRP), Ayres or combinations of these methods, were investigated.[16] Best-evidence synthesis showed moderate evidence for a reduced length of hospital stay in favour of MRP or traditional care compared with an impairment-focused neuromuscular treatment approach such as Bobath.[17-19] No evidence was found for applying a specific neurological treatment programme in terms of muscle strength[20,21], synergism[22], muscle tone[23], walking ability[23], dexterity[17,24,25] or ADL[17,18,20,21,23,25-27]. Hafsteinsdóttir reported a similar finding for nursing care in hospitalised stroke patients. The NDT-approach was not found to be an effective method and therefore she encouraged health care professionals to reconsider the use of the NDT-approach.[28]

Impairment-focused programmes fail to generate functional improvements. These programmes include biofeedback, neuromuscular or transcutaneous nerve stimulation, cardiovascular fitness training and muscle strengthening.[16] Moreover, this review indicates that the rational for different treatment approaches is still weak. However, strong evidence was found for therapies that administered functional training, such as constraint-induced movement therapy, treadmill training with or without body weight support, aerobics, external auditory rhythms during gait and neuromuscular stimulation for glenohumeral subluxation.[16]

Another systematic review investigated the outcomes of progressive resistance strength training following stroke.[29] From the 350 publications initially identified, eight met the inclusion criteria of the review. Only three were randomized trials and the remainder were single-case time-series analyses or pre-experimental trials. The authors concluded that there is preliminary evidence that progressive resistance strength training reduces musculoskeletal impairment after stroke, but they were unable to demonstrate effects on enhancing performance of functional activities or participation in societal roles.[29] Yet another systematic review of exercise trials after stroke identified insufficient evidence to establish a positive effect of cardiovascular exercise on disability, impairment, extended ADL, quality of life and case fatality.[30] From the 18,934 potential relevant trials identified 16 trials were found to meet the inclusion criteria. Ultimately, information from only three trials, all with different outcome measures, was used for the review as poor methodological quality necessitated to disregard the other studies.

A meta-analysis subsequently provided evidence for the use of increased intensity of task-specific exercise therapy as a means of achieving faster motor recovery after stroke.[31] A random effects model adjusted for the difference in treatment intensity in each study was used. Twenty of the 31 candidate studies, involving 2,686 stroke patients, were included in the synthesis. Small but statistically significant weighted mean differences (WMD) were found for ADL measured at the end of the intervention phase. Further analysis showed a significant homogeneous WMD for the effects of increased exercise intensity, ie, augmented therapy for at least 16 hours within the initial 6 post-stroke months, on instrumental ADL and gait speed. The authors concluded that there is strong evidence that patients benefit from exercise programmes in which functional tasks are directly and intensively trained.[31]

Following discharge from a stroke service treatments are often continued albeit less frequently. According to a Cochrane review outpatient rehabilitation may prevent deterioration in seven of every 100 patients residing in the community.[32] This rehabilitation is directed to the restoration of motor control in gait and gait-related activities, improvement of upper extremity function, teaching the patient to cope with existing deficits in ADL and enhancement of participation in general.

Based on multidisciplinary consensus guidelines have also been developed in many countries for overall stroke care[e.g.33] and stroke rehabilitation.[e.g.34] Adherence to these guidelines has been shown to be related to functional recovery. Greater levels of adherence to postacute stroke rehabilitation guidelines are associated with improved patient outcomes[35] and patient satisfaction.[36] Compliance with guidelines may be viewed as a quality-of-care indicator with which to evaluate new organizational and funding changes involving postacute stroke rehabilitation.

METHODOLOGICAL QUALITY OF STROKE REHABILITATION RESEARCH

What these systematic reviews also demonstrate is the poor methodological quality of many intervention studies. These studies either failed to meet the inclusion criteria by design and thus were not included in the analysis or lacked statistical and internal validity. Ottenbacher and Jannell found that standardized mean differences (ie, effect sizes) of poorly designed trials were twice as large (ie, 0.73 versus 0.38 standard deviation units) when compared to those of well designed intervention trials.[37] Quite often the observer was not independent of treatment assignment.[38] In addition it has been claimed that insensitivity of most ordinal scaled measurement instruments jeopardises the detection of relatively small effects of stroke rehabilitation. Matyas and Ottenbacher also noticed a lack of power of intervention studies in the detection of differences in efficacy.[39] When there are large differences in patient characteristics and individual recovery patterns within both the experimental and control groups it becomes difficult to demonstrate differences between groups, in particular when these effects of treatment are small compared to the extent and heterogeneous nature of developing spontaneous recovery. For this reason a number of researchers advocate the inclusion of a large number of patients in stroke rehabilitation trials, whereas others prefer controlled single subject experimental designs or interrupted time series experiments.[40-42] A major advantage to this latter design is its control for subject homogeneity. However, it should be noted that there are also some inherent disadvantages to controlled single subject experimental designs in that systematic variance may be induced by initial patient selection, carry over effects of treatment conditions from preceding phases onto ensuing phases, training effects of repeated measurements, contamination by differences in circumstances during the study, and confounding effects generated by non-specific parts of the treatment.[40,43] In addition single subject experimental designs may suffer from the unknown natural history of individual subjects.[44] To overcome the problem of heterogeneity within the stroke population several authors have suggested that the implementation of well-defined criteria for patient selection may improve statistical power and concomitant conclusion validity in stroke rehabilitation trials conducted to detect differences in efficacy.[45-48]

Alternative methods of experimental control accomplish efficient treatment comparisons at the individual patient level. To control for spontaneous recovery after the subacute phase multiple baseline design studies are useful in demonstrating immediate short lasting effects.[49] In cross-over and single subject designs patients act as their own control thus reducing attrition from patients randomized to the control group. Another advantage of these designs is that they require fewer participants. Although by definition, single subject designs have low generalizability, if done well, they are controlled and can provide very specific answers. This information can than be used for further scientific scrutiny in clinical randomized trials.[50]

MEASUREMENT AND PREDICTION IN STROKE

When based on high quality studies systematic reviews and meta-analyses provide the ultimate evidence upon which evidence based practice is built. This evidence is based upon the (pooled) weighted mean differences of several RCTs and CCTs designed to study the effects of specific therapeutic interventions. The goal of these trials is to elucidate the benefits generated by specific interventions which eventually may lead to the development of efficient and effective rehabilitation programmes for acute and chronic stroke patients. These training programmes are likely to produce better results if they comply with the principles of motor learning. Motor learning is defined as a relatively permanent change in the capability for responding associated with practice or experience.[51] Task-specificity, practice, goal-setting, feedback and motivation are considered important elements in motor learning.[51] In practice it appears that repetition alone is less effective than repetition with variable practice. Many rehabilitation studies report immediate posttraining gains, particularly if they used physical conditioning principles. Therefore, immediate posttraining changes are considered 'performance gains' that can only be assessed as re-learned if sufficient time has elapsed to allow the gains to become permanent.[52] This implies that stroke patients require long term follow-up and assessment in order to demonstrate rehabilitation induced effects. Moreover, this approach also allows for revealing any time-course related effects. To date, many time dependent variables are yet to be determined. However, time itself appears to be one of the most important – although neglected - determinants in relation to spontaneous functional recovery.[53]

Findings from longitudinal studies with repeated measurements over time indicate that recovery of neurological impairment and disability shows a nonlinear pattern as a function of time.[54-59] Such research employs a dynamic model which reflects reality more accurately and validly as time is likely to confound reported predictive relationships in cross sectional research. It may even address important issues such as elucidating the critical time window for therapy in stroke recovery. Moreover, predicting outcome at an early post-stroke stage allows for the development of optimal individual tailored treatments and early discharge planning. For instance, in a paper describing the probability of regaining dexterity in the flaccid upper limb it was reported that optimal arm function at 6 months could be predicted within 4 weeks after onset based on Fugl-Meyer scores of the flaccid arm.[60] Furthermore, it was found that lack of voluntary motor control of the leg in the first week with no emergence of arm synergies at 4 weeks was associated with poor outcome at 6 months.[60] The outcome of prediction models assists the practitioner in making a proper prognosis and treatment plan for an individual stroke patient. This process, known as clinical reasoning or clinical decision making, is characterized by the

gathering and interpretation of information obtained from a patient, the estimation of expected treatment effects and subsequently the formulation of predictions regarding functional outcome. Unfortunately, studies describing adequate prediction models for recovery of gait after stroke are relatively scarce and of poor quality. A systematic review on prognostic factors for ambulation and ADL in the subacute phase after stroke involving 26 studies with 7,850 patients found only one prognostic factor (incontinence for urine) identified in three level A studies (ie, good level of scientific evidence according to the methodological score). However, they concluded that at present insufficient methodological quality of selected publications did not allow for an evidence-based prediction of ADL and ambulation in the subacute stage of stroke.[61]
Ideally, the development of a new prediction model should be based on established guidelines and the accuracy of a model's predictions must be externally validated in at least one independent cohort of stroke patients that was not used to generate the model.[62] Predictor variables must be easy to collect, clinically relevant and reliable. Basically, such a newly developed prediction model could suffer from three types of error: overfitting, ie, too many variables in the model, results in the erroneous inclusion of false positive predictors (type I error); underfitting, ie, too few variables in the model, is responsible for the omission of important variables (type II error) and paradoxical fitting. This represents a reported negative association with outcome when in fact this association is positive (type III error). The risk of these problems increases as the ratio of outcome events to the number of predictor variables becomes smaller. The risk of error is especially high with an events per variable (EPV) ratio of <10 for binary outcomes.[62]

The use of clinimetrics is of vital importance in this process.[63] The systematic assessment of longitudinal changes based upon clinimetric sound measurement instruments improves objectivity and facilitates communication among and between professionals and caregivers. In stroke research, with its large clinimetric 95% error thresholds and its dominating dynamics in recovery profiles as a result of underlying mechanisms of spontaneous recovery, longitudinal applied clinimetric measures will create a valid representation of any post-stroke changes that may have occurred. The information based on these measurements will generate a recovery profile of individual patients which allows for an estimation of the relationship between impairments, activities and participation levels and contributes to the identification of risk factors that can be used in the discrimination between stroke patients with good and poor prognosis. It can guide patient management by providing a foundation on which realistic and attainable short and long term therapeutic goal setting and discharge planning can be implemented. Retrospectively, it allows for a reflection on the impact of treatment decisions made during the course of recovery. A learning process is thus created that may benefit the care of future stroke patients.[64]

DISCUSSION

The objective of stroke rehabilitation is to enable individual patients to achieve their full potential and to maximize the benefits from training in order to attain the highest possible degree of physical and psychological performance. The ultimate goals for many stroke patients is to achieve a level of functional independence necessary for returning home and to integrate as fully as possible into community life. For this reason clinicians are challenged to reliably predict at an early post-stroke stage the degree of disability the patient will ultimately experience in order to facilitate optimal stroke rehabilitation and appropriate discharge planning and implementation of resources. Still a gap remains between prognostic research and rehabilitation practice. Therapists and physicians need to formulate their functional goals as precisely as possible. This requires adequate knowledge of the patient and disease characteristics that determine functional outcome. Making a proper prognosis is far more complex than just applying a suitable prediction model and incorporates clinical decision making or clinical reasoning based on recovery milestones, such as sitting balance, standing upright and the ability to walk.[65] Although adherence to major methodological principles in prognostic research is a prerequisite for achieving internal and statistical validity, the heterogeneity of the stroke population remains a major threat to the external validity of prediction models. Therefore, stratification of patients based on demographic and diagnostic data has been recommended in order to increase precision of prediction models. The aim of applying prediction models in more specific subpopulations of stroke patients is to strike a balance between precision and generalizability. In order to achieve the most efficient use of stroke services, it is important to identify predictors that discriminate between stroke patients with good and poor prognosis. Differences within and between studies in post-stroke timing of measurements taken for prediction decrease external validity of existing prediction models. The strict adherence to adequate study designs, restrictive selection criteria and repeated measurements over time, based on clinimetric sound instruments, can contribute to a better understanding of stroke recovery in general and patient characteristics that allow for an early reliable prediction of the final outcome. Only than individually tailored optimal treatment programmes can be implemented.

Traditionally, cross-sectional stroke research is conducted. However, the variability in timing of the assessment of final outcome has made comparisons between prognostic studies difficult. This presents a problem in systematic reviews as the lack of uniformity limits mutual comparison let alone the pooling of results for meta-analysis. In stroke research the nonlinear functional recovery pattern presents challenges to overcome and calls for an inception cohort with repeated measurements taken at fixed times post-stroke. A major advantage of frequently repeated measurements over time is that it represents reality far better than one or two measurements. Instead of relying on one or two images of the patients' functional status frozen in time for analysis several closely sequential images over time can be observed and analyzed thus providing insight into the dynamics of recovery. This in turn allows for a more valid interpretation of reality as it enables observing changes in actual recovery processes that take place over time. More research is needed for the development of prognostic models based on the within-subject variability of covariates and uniform timing of prediction and assessment of final outcome. Future research should also focus on identifying time dependent determinants. This information can than be used to determine critical time windows for specific therapeutic interventions but may also assist in identifying hierarchy in recovery patterns.[53] The use of mixed modeling statistical techniques allows for analyzing cross-sectional and longitudinal treatment and time effects simultaneously while correcting for the correlated observations within subjects over time and allowing for regression coefficients to differ between subjects. As time constitutes an independent covariate in such a model these statistical methods enable longitudinal analysis of unequally spaced time points of measurement. Moreover, in random coefficient analysis missing data are presumed to be missing at random.[66] Finally, there are strong indications that motor recovery after stroke occurs to a large extent through behavioural compensation, rather than via processes of 'true recovery' alone.[67] Future studies may explore the relationship between behavioural adaptations and improved skills after stroke ie, addressing the issue of which changes in motor control coincide with functional improvements. This knowledge may contribute to determining the best way in which to subject stroke patients to therapeutic exercises.

REFERENCES

1. Association AH. Heart disease and stroke statistics-2003 update. Dallas, TX: American Heart Association. 2002.
2. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R. The greater Cincinnati / Northern Kentucky stroke study. Stroke. 1998; 29: 415-421.
3. Elkins JS, Johnston SC. Thirty-year projections for deaths from ischemic stroke in the United States. Stroke. 2003; 34: 2109-12.
4. Murray JL, Lopez AD, ed. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020, Cambridge, Mass: Harvard University Press. 1996.
5. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk. A meta-analysis. Stroke. 2003; 34: 2475-2482.
6. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2002; 1: CD000197.
7. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: Evidence, costs, and effects on individuals and populations. Lancet. 1999; 354: 1457-63.

8. Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke. 2001; 32: 268-74.
9. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2002; 1: CD000197.
10. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. Lancet. 1999; 354: 1457-63.
11. Langhorne P, Pollock A. What are the components of effective stroke unit care? Age Ageing. 2002; 31: 365-71.
12. Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke. 2001; 32: 268-74.
13. Gresham GE, Duncan PW. Statson WB. 'Priorities for future research'. Clinical practice guidelines number 16, US department of health and human services, Agency for health care policy and research, Rockwell, Maryland, AHCPR publication. 1995; no. 95-0662.
14. Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke. 2001; 32: 268 –274.
15. Sherrington C, Herbert RD, Maher CG, Moseley AM. PEDro. A database of randomized trials and systematic reviews in physiotherapy. Man Ther. 2000; 5: 223-26.
16. Peppen van RPS, Kwakkel G, Wood-Dauphinee S, Hendriks HJM, Van der Wees PhJ, Dekker J. The impact of physical therapy on functional outcome after stroke: What's the evidence? Clin Rehabil. 2004; 18: 833-862.
17. Langhammer B, Stanghelle JK. Bobath or motor relearning programme? A comparison of two different approaches of physiotherapy in stroke rehabilitation: a randomized controlled study. Clin Rehabil. 2000; 14: 361-69.
18. Lord JP, Hall K. Neuromuscular re-education versus traditional programmes for stroke rehabilitation. Arch Phys Med Rehabil. 1986; 67: 88-91.
19. Patel M, Potter J, Perez I et al. The process of rehabilitation and discharge planning in stroke: a controlled comparison between stroke units. Stroke 1998; 29: 2484-87.
20. Logigian MK, Samuels MA, Falconer J et al. Clinical exercise trial for stroke patients. Arch Phys Med Rehabil. 1983; 64: 364-67.
21. Stern PH, McDowell F, Miller JM et al. Effects of facilitation exercise techniques in stroke rehabilitation. Arch Phys Med Rehabil. 1970; 51: 526-31.
22. Poole JL, Whitney SL, Hangeland N et al. The effectiveness of inflatable pressure splints on motor function in stroke patients. Occup Ther J Res. 1990; 10: 360-66.

23. Dickstein R, Hocherman S, Pillar T et al. Stroke rehabilitation. Three exercise therapy approaches. Phys Ther. 1986; 66: 1233-38.
24. Basmajian JV, Gowland CA, Finlayson MA et al. Stroke treatment: comparison of integrated behavioral-physical therapy vs traditional physical therapy programmes. Arch Phys Med Rehabil. 1987; 68: 267-72.
25. Gelber DA, Josefczyk PB, Herrman D et al. Comparison of two therapy approaches in the Impact of physical therapy after stroke 855 rehabilitation of the pure motor hemiparetic stroke patients. J Neuro Rehab. 1995; 9: 191-96.
26. Jongbloed L, Stacey S, Brighton C. Stroke rehabilitation: sensorimotor integrative treatment versus functional treatment. Am J Occup Ther. 1989; 43: 391-97.
27. Mudie MH, Winzeler-Mercay U, Radwan S et al. Training symmetry of weight distribution after stroke: a randomized controlled pilot study comparing task-related reach, Bobath and feedback training approaches. Clin Rehabil. 2002; 16: 582-92.
28. Hafsteinsdóttir TB, Algra A, Kappelle LJ, Grypdonck MH; Dutch NDT Study Group. Neurodevelopmental treatment after stroke: a comparative study. Journal of Neurology, Neurosurgery & Psychiatry. 2005; 76: 788-92.
29. Morris SL, Dodd KJ, Morris ME. Outcomes of progressive resistance strength training following stroke: a systematic review. Clinical Rehabilitation. 2004; 18: 27-39.
30. Meek C, Langhorne P. A systematic review of exercise trials post stroke. Clinical Rehabilitation. 2003; 17: 6-13.
31. Kwakkel G, Peppen van R, Wagenaar RC, Wood Dauphinee S, Richards C, Ashburn A, Miller K, Lincoln N, Partridge C, Wellwood I, Langhorne P, Effects of augmented exercise therapy time after stroke. A meta-analysis. Stroke. 2004; 35: 2529-2536.
32. Outpatient Service Trialists. Therapy-based rehabilitation services for stroke patients at home. Cochrane Database Syst Rev. 2003; 1: CD002925.
33. Adams HP, Adams RJ, Brott T, Zoppo del GJ, Furlan, A; Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ. Guidelines for the early management of patients with ischemic stroke. A scientific statement from the Stroke Council of the American Stroke Association. Stroke. 2003; 34: 1056 – 1083.
34. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. 2002.

35. Duncan PW, Horner RD, Reker DM, Samsa GP, Hoenig H, Hamilton B, LaClair BJ, Dudley TK. Adherence to postacute rehabilitation guidelines is associated with functional recovery in stroke. Stroke. 2002; 33: 167-178.
36. Reker DM, Duncan PW, Horner RD, Hoenig H, Samsa GP, Hamilton BB, Dudley TK. Postacute stroke guideline compliance is associated with greater patient satisfaction. Arch Phys Med Rehabil. 2002; 83 (6): 750-756.
37. Ottenbacher KJ, Jannell S. The results of clinical trials in stroke rehabilitation research. Archives of neurology. 1993; 50: 37-44.
38. Schultz KF, Calmers I, Hayes RJ, Altman DG. Empirical evidence of bias. JAMA. 1995; 273: 408-412.
39. Matyas TA, Ottenbacher KJ. Confounds of insensitivity and blind luck: Statistical conclusion validity in stroke rehabilitation clinical trials. Archives of physical medicine and rehabilitation. 1993; 74: 559-565.
40. Wagenaar RC. Functional recovery after stroke. VU University press Amsterdam 1990.
41. Gonella C. Designs for clinical research. Physical Therapy. 1973; 53: 1276-1283.
42. Hayes SC. Single subject research strategies in occupational clinical practice. Journal of consultation and clinical psychology. 1981; 50: 193-211.
43. Wagenaar RC, Meyer OG, Van Wieringen PCW, Kuik DJ, Hazenberg GJ, Lindeboom J, Wichers F, van Rijswijk H. The functional recovery of stroke. A comparison between neurodevelopmental treatment and the Brunnstrom method. Scandinavian Journal of Rehabilitation Medicine. 1990; 22: 1-8.
44. Basmajian JV, Gowland CA. The many hidden faces of stroke: A call for action. Archives of physical medicine and rehabilitation. 1987; 68: 319.
45. Jongbloed L. Prediction of function after stroke: a critical review. Stroke. 1986; 17: 765-776.
46. Gresham GE. Past achievement and new directions in stroke outcome research. Stroke. 1990; 21 (II supplement), 1S-3S.
47. Gladman JRF, Harwood DMJ, Barer DH. Predicting the outcome of acute stroke: prospective evaluation of five multivariate models and comparison with single methods. Journal of Neurology, neurosurgery and psychiatry. 1992; 55: 347-351.
48. Hier DB, Edelstein G. Deriving clinical prediction rules from stroke outcome research. Stroke. 1991; 22: 1431-36.
49. Kazdin AE. Single-Case Research Designs. Oxford University Press. 1982.

50. Zhan S, Ottenbacher KJ. Single subject research designs for disability research. Disabil Rehabil. 2001; 23: 1-8.
51. Schmidt RA, Lee T. Motor control and learning. Champaign, IL. Human kinetics. 1999.
52. Winstein CJ. Knowledge of results and motor learning – implications for physical therapy. Physical Therapy. 1991; 71: 140-9.
53. Kwakkel G. Dynamics in functional recovery after stroke. Ponsen & Looijen BV, The Netherlands. 1998.
54. Heller A, Wade DT, Wood VA, Sunderland A, Langton Hewer RL. Arm function after stroke: measurement and recovery over the first three months. J Neurol Neurosurg Psychiatry. 1987; 50: 714–719.
55. Wade DT, Langton Hewer RL, Wood VA, Skilbeck CE, Ismail HM. The hemiplegic arm and recovery. J Neurol Neurosurg Psychiatry. 1983; 46: 521–524.
56. Sunderland A, Tinson DJ, Bradley L, Langton Hewer RL. Arm function after stroke: an evaluation of grip strength as a measure of recovery and prognostic indicator. J Neurol Neurosurg Psychiatry. 1989; 52: 1267–1272.
57. Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995; 76: 27–32.
58. Loewen SC, Anderson BA. Predictors of stroke outcome using objective measurement scales. Stroke. 1990; 21: 78–81.
59. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke: outcome assessment and sample size requirements. Stroke. 1992; 23: 1084–1089.
60. Kwakkel G, Kollen BJ, Grond van der J, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb: Impact of severity of paresis and time since onset in acute stroke. Stroke. 2003; 34: 2181-2186.
61. Meijer R, Ihnenfeldt DS, de Groot IJ, van Limbeek J, Vermeulen M, de Haan RJ. Prognostic factors for ambulation and activities of daily living in the subacute phase after stroke. A systematic review of the literature. Clin Rehabil. 2003; 17 (2): 119-129.
62. Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke. Development and validation of new prognostic models. Stroke. 2002; 33: 1041-1047.
63. Feinstein AR. Clinimetrics. Yale University Press. New Haven. 1987.

64. Koolstra M, Burgers-Bots IAL, Lemmens CJ, Smeets CJ, Kwakkel G. Klinimetrie na een beroerte. Een praktische handleiding. VU medisch centrum 2001.
65. Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation - A critical review of the literature. Physiotherapy. 1999; 85 (7): 377-391.
66. Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology. Cambridge University Press. 2003.
67. Kwakkel G, Kollen BJ, Lindeman E. Understanding the pattern of functional recovery after stroke: Facts and theories. Restorative Neurology and Neuroscience. 2004; 22: 281-299.

CHAPTER 3

Hemiplegic gait after stroke:
Is measurement of maximum speed required?

Boudewijn Kollen, Gert Kwakkel, and Eline Lindeman

Archives of Physical Medicine and Rehabilitation 2006; 87: 358-363

Abstract

OBJECTIVE:

To study the relation between comfortable and maximum walking speed in stroke rehabilitation and to determine which parameters are predictive in this relationship and increase its precision.

DESIGN:

One-year prospective cohort study. Longitudinal information was obtained for 10-m comfortable and maximum walking speeds, hemiplegic limb muscle strength, and balance. In addition, subjects' ages and the type of rehabilitation they received were registered.

SETTING:

Stroke service facilities.

PARTICIPANTS:

Eighty-one acute stroke patients.

MAIN OUTCOME MEASURE:

Ten meter maximum walking speed.

RESULTS:

We found a progressive improvement in walking speed and a mean systematic difference between comfortable and maximum walking speeds. An overall mean intraclass correlation coefficient for consistency of ρ equal to .96 and a within- and between-subject regression coefficient of 1.32 were demonstrated for the relation between comfortable and maximum walking speeds. None of the covariables were statistically significant in the final linear regression prediction model.

CONCLUSIONS:

Independent of time after onset of stroke, maximum walking speed can be predicted by comfortable walking speed with considerable accuracy. The precision of this estimation is not increased by considering patients' age, hemiplegic muscle strength, balance or therapeutic intervention.

INTRODUCTION

Clinically, it is widely accepted that walking speed is a simple but highly reliable and responsive parameter of gait. [1,2 (page 78,79)] Reliability has been established for test-retest and between-observer measurements.[3,4] Repeated measurements with a simple timed walking test has been qualified as a responsive method to measure change in walking performance over time.[5] Several randomized-controlled trials (RCTs) have demonstrated favourable effects of gait training, particularly on walking speed.[6-10] Supporting the validity of speed measurement as an useful tool for objectively monitoring progress in hemiplegic gait, statistical evaluations have found significant correlations between time-distance parameters such as cadence, cycle time, stance time, swing time, stride length, and step length and walking speed[11-13] as well as ambulatory performance.[1,3,11,13-18] In addition, gait speed correlates strongly with other parameters such as balance[19], use of walking aids[3] and number of falls; it also reflects activities of daily living function in geriatric patients.[20]
Given this body of evidence it is suggested that improvement in walking speed reflects a genuine improvement in mobility, even if other mostly categorical measures fail to detect it.
Obtaining sufficient information on adequate walking speed requires the recording of both comfortable speed and maximum walking speed, because the latter may be important in community based activities such as crossing a street. Because most patients with stroke tend to walk slowly it is necessary to determine to what safe level they are capable of increasing their walking speed. Bohannon[17] studied this relation cross sectionally in 20 subacute stroke patients and found Spearman rank-order correlation coefficients for Functional Independence Measure (FIM) scores of .826 (p <.001) and .673 (p <.01) for comfortable and fast walking speed measurements, respectively, and a 1.40 linear regression coefficient for comfortable speed versus maximum walking speed. This latter finding denotes its clinical relevance, in that 1.4 times the comfortable speed corresponds with the maximum speed.

In this study we elaborate on these findings by investigating the predictive relation between comfortable and maximum walking speed at regular post-onset times in a larger group of stroke patients. Therefore, we addressed the following research questions:

1. Can maximum walking speed be accurately predicted by comfortable walking speed in patients with severe stroke?
2. Can the precision of this possible predictive relationship be increased by considering a stroke patient's age, hemiplegic limb muscle strength, balance and his/her therapeutic intervention?
3. Is the relation between comfortable and maximal walking speed stable over time?

MATERIALS AND METHODS

Design and procedures

This prospective cohort study was part of a 3 group randomised clinical trial conducted to study the effects of augmented exercise training on stroke outcome.[21] Within 14 days after stroke onset, 101 severely disabled patients with a primary middle cerebral artery stroke were randomly assigned to a basic rehabilitation programme that was supplemented with additional arm or leg training, or to a control programme in which the arm and leg were immobilized with an inflatable pressure splint. Each treatment regimen was applied for 30 minutes, 5 days a week during the first 20 weeks after stroke.

Patients were included when they met the following criteria: 1) were between 30 and 80 years old; 2) had suffered an ischemic, first-ever, stroke involving the middle cerebral artery as revealed by CT- or MRI-scan; 3) were unable to walk at first assessment; 4) had no complicating medical history such as cardiac, pulmonary or orthopedic disorders; 5) had no severe deficits in communication, 6) had no severe deficits in memory and understanding; and 7) provided written or verbal informed consent and demonstrated sufficient motivation to participate. Details of design and outcome have been published elsewhere.[21] Inclusion in this study subset was also contingent on one’s ability to walk 10m without the physical assistance of a therapist.

Measurements

Functional Ambulation Categories (FAC)

Walking ability was assessed with the Functional Ambulation Categories.[2] The FAC is a reliable and valid assessment tool that includes 6 categories designed to provide information on the level of physical support needed by patients to ambulate safely. The first measurement of gait speed was taken as soon as the patient could walk 10m without physical assistance while under the supervision of a therapist. This criterion corresponds to FAC level 3.[3,4] Walking devices were allowed during the measurements, with the exception of a rollator or walker. Measurements began within 14 days of stroke onset, and were done weekly up to 10 weeks, fortnightly up to 20 weeks, and thereafter only at 26, 38 and 52 weeks after onset. All functional assessments were done by one observer (GK) who was blinded to subjects’ treatment assignment.[21]

Speed

We studied gait speed at comfortable and safe maximum walking speeds using a standard approach to assess gait performance.[3,16] To reduce measurement error of timed walking test, we calculated the mean of three repeated measurements.[22] During each session, the patient walked 10m at a comfortable and at a maximum pace. Timing with a digital stopwatch that registered time in 1/100 of a second was manually initiated at the "go" instruction and stopped when the subject crossed the 10-m mark. The patient rested for about one minute between each test. Registered speed was subsequently converted into meters per second by dividing the distance walked by the time required. No encouragement to facilitate performance during a walking session was permitted.

Motricity index (MI)

Recovery of strength in upper extremity and lower extremity was assessed with the Motricity index.[23] This instrument reliably assesses paresis in the upper and lower extremities of stroke patients. It uses a weighted score of a maximum of

100 points for each extremity and is derived from the Medical Research Council (MRC) grades. It tests 6 limb movements.

Timed balance test (TBT)

Balance was measured with the timed balance test.[24] This instrument has 5 components on an ordinal scale and measures timed balance on progressively diminishing support surfaces.

In addition to a basic rehabilitation programme, patients received one of three therapeutic interventions that emphasized upper- or lower-extremity training or air splint immobilization of the upper and lower limb.[21]

Age, hemiplegic limb muscle strength, balance, and therapy are believed to be related to walking ability. We used these parameters as predictive co-variables in the linear regression model to increase the precision of the prediction of the relation between comfortable and maximum walking speed.[25]

Statistical analysis

We applied cross-sectional and longitudinal analysis for all included measurements and we used Cronbach's Alpha coefficients to determine internal consistency of repeated measurements. We conducted paired Student *t* testing to demonstrate systematic differences between both speeds. Two-way Intraclass Correlation coefficients for Consistency ($ICC_{consistency}$) were calculated to test the relative agreement between comfortable and maximum walking speeds at each measurement.

Research question 1:

The predictive relation between comfortable and maximum walking speeds was investigated cross sectionally by applying a linear regression model, using maximum walking speed as the dependent and comfortable walking speed as the independent variable.

Research question 2:

Covariables were added to this model to increase precision of prediction. Entering of covariables into the linear regression model was based upon the stepwise backward selection technique at α equal to 0.05. These variables included age, motricity index of arm and leg, timed balance test and applied therapeutic intervention. Compliance with the assumptions of the linear regression model was confirmed for all variables involved. We used a two-tailed significance level of .05 for all tests.

Research question 3:

Finally, we applied random coefficient analysis to obtain a single coefficient reflecting within- and between-subject regression for all measurements, again using maximum walking speed as the dependent variable and comfortable walking speed as the independent variable. This method analyzes cross-sectional and longitudinal treatment and time effects simultaneously while correcting for the correlated observations within subjects over time. It allows for regression coefficients to differ between subjects. Because time constitutes an independent covariate in such a model, this statistical method makes possible longitudinal analysis of unequally spaced time points of measurement. Finally, in random coefficient analysis, missing data are presumed to be missing at random.[26]

RESULTS

Patient characteristics are presented in Table 1. The mean interval (± standard deviation: SD) between stroke onset and first unassisted walk (FAC ≥3) was 4.8 ±2.9 weeks. None of the patients could walk unassisted in the first week post-stroke. Because not all 101 patients progressed to unassisted walking at some point, comfortable walking speed was measured in 85 patients and maximum walking speed in 81 patients. Therefore, our study results were based on a subset population of a maximum of 81 subjects. The mean comfortable walking speed progressively increased from the 2nd to the 52nd week from .037 to .635 m/s; mean maximum speed increased from .071 to .851 m/s (Figure 1). The overall mean comfortable and maximum speed was .472 and .638 m/s, respectively.

Internal consistency of repeated measurements yielded high coefficients for comfortable walking speed (α = .98), maximum walking speed (α = .99), motricity index of arm (α = .99), motricity index of leg (α = .99) and timed balance test (α = .97).

Table 1. Patient characteristics measured within two weeks after stroke.

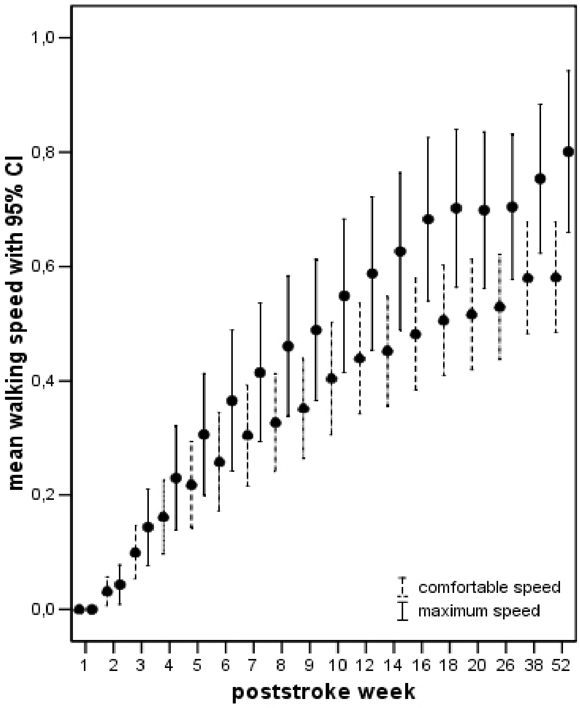
Group	Total (±SD)
Number	81
Sex (F/M)	34/47
Age, years	64.3 (10.8)
MMSE (0-30)	26.6 (2.3)
Stroke hemisphere (L/R)	33/48
Type of Stroke: (OCSP)	
TACI (0/1)	43
PACI (0/1)	31
LACI (0/1)	7
OPS (1.6-6.8)	4.2 (0.9)
GCS (0-15)	14.8 (0.9)
(Cognitive) impairments (%)	
Visual inattention (0/1)	45.7
Hemianopia (0/1)	25.9
Visual gaze deficit (0/1)	21.0
Number of days between CVA and first measurement (±SD)	8.2 (2.7)
MI-lower extremity (0-100)	33.0 (28.4)
TCT (0/200)	61.84 (28.3)
Brunnstrom (1-6)	2.53 (1.4)
Comfortable walking speed (m/s)	0.04 (0.1)
BI (0-20)	6.90 (3.7)
FAC (0-5)	0.89 (1.0)

NOTE. Values are N or mean ± standard deviation (SD) or as indicated.
Abbreviations: CVA, cerebrovascular accident; GCS, Glasgow Coma Scale; LACI, Lacunar Anterior Circulation Infarcts; MMSE, Mini-Mental State Examination; OCSP, Oxford Community Stroke Project; OPS, Orpinton Prognostic Scale; PACI, Partial Anterior Circulation Infracts; TACI, Total Anterior Circulation Infarcts; TCT, Trunc Control Test.
*(0/1) equals no/yes

A paired *t* test revealed systematic differences between comfortable and maximum gait velocities (Table 2). The distribution of these measurement differences within the 95% limits of agreement decreased as more patients entered the study (Figure 2).

$ICC_{consistency}$ values were calculated for the relation between comfortable and maximum walking speeds at each measurement and the overall mean (ie, the mean of all comfortable and maximum walking speed measurements) and are presented in a scatter plot (Table 2 and Figure 3). There was increased measurement error toward the highest speeds, while there was decreased discrimination between measurements at lower speeds. Significance for all ICC measurements was obtained at the *p* equal to .000.

Figure 1. Distribution of mean comfortable and maximum walking speeds with 95% confidence intervals over time after stroke.



Research question 1:

All linear regression coefficients were significant (Table 3) and, on average, there was a regression coefficient of 1.43 (CI: 1.37 – 1.49, p = .000).

Research question 2:

Covariables added to the final regression models were not significant and therefore did not contribute to the precision of the cross-sectional relation between comfortable and maximum walking speed.

Figure 2. A Bland & Altman plot adapted for differences in comfortable and maximum walking speed post-stroke measurements. Initial measurement differences are large but gradually diminish with subsequent enrolment of patients (learning effect).

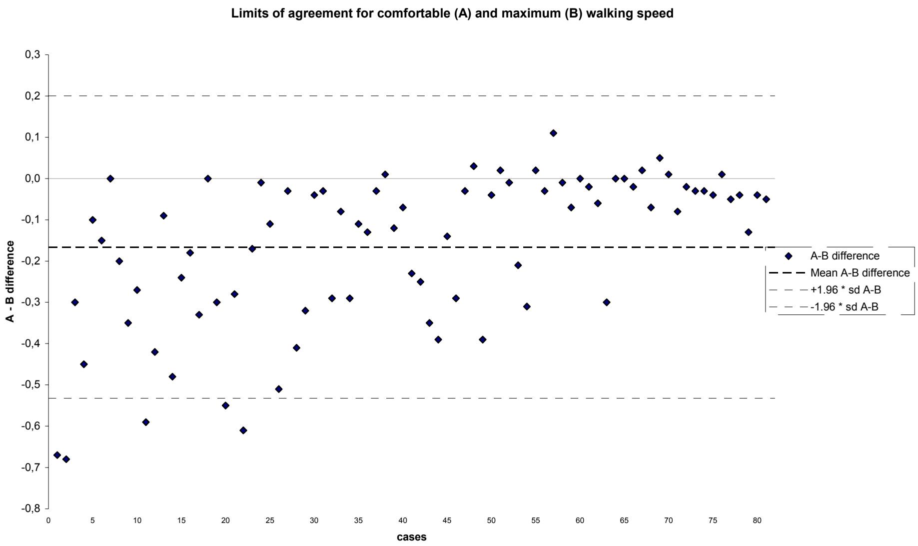
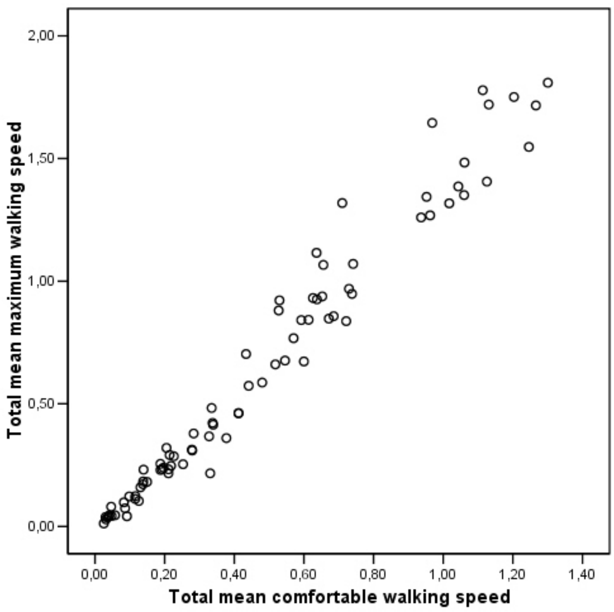


Figure 3. A scatter plot showing the poststroke relationship between overall means (in m/s) of comfortable and maximum walking speed ($ICC_{consistency}$, ρ = .96). This plot clearly shows decreased discrimination between measurements at lower speeds and increased scattering (measurement error) at higher speeds.



Research question 3:

Random coefficient analysis produced a significant within and between subject regression coefficient of 1.32 (CI: 1.29 – 1.36, p = .000) with fixed and random intercept and slope indicating that 1.32 times the comfortable walking speed generated the expected maximum walking speed.

Table 2. Results of paired Student t test, two way $ICC_{consistency}$ for comfortable, and maximum gait speeds.

Week	N	Mean difference (CI)	SD	t	ρ* (CI)
2	74	-.033 (-.063 - -.003)	.129	-2.21	.86 (.78 - .91)
3	78	-.060 (-.100 - -.020)	.178	-2.99	.94 (.90 - .96)
4	78	-.083 (-.128 - -.038)	.199	-3.69	.95 (.92 - .97)
5	79	-.102 (-.148 - -.057)	.202	-4.50	.96 (.94 - .97)
6	76	-.090 (-.128 - -.052)	.168	-4.69	.97 (.95 - .98)
7	75	-.110 (-.160 - -.060)	.218	-4.37	.96 (.93 - .97)
8	78	-.147 (-.204 - -.089)	.255	-5.09	.94 (.91 - .96)
9	79	-.159 (-.206 - -.112)	.211	-6.71	.96 (.94 – 98)
10	75	-.150 (-.208 - -.091)	.253	-5.12	.95 (.92 - .97)
12	72	-.175 (-.231 - -.120)	.237	-6.27	.96 (.93 - .97)
14	72	-.196 (-.253 - -.139)	.242	-6.86	.95 (.92 - .97)
16	73	-.212 (-.270 - -.153)	.253	-7.16	.95 (.92 - .97)
18	71	-.199 (-.251 - -.147)	.220	-7.63	.96 (.93 - .97)
20	72	-.190 (-.241 - -.139)	.219	-7.37	.96 (.93 - .97)
26	73	-.187 (-.254 - -.121)	.285	-5.63	.93 (.88 - .95)
38	71	-.191 (-.234 - -.148)	.181	-8.89	.97 (.95 - .98)
52	69	-.213 (-.274 - -.152)	.253	-6.98	.94 (.90 - .96)

NOTE. All paired Student t test outcomes were significant at the p = 0.00 level, except for week 2 (p = 0.030) and week 3 (p = 0.004).
* ICC

DISCUSSION

Our results show that, in stroke patients with marked hemiplegia, maximum walking speed can be reliably estimated by measuring comfortable walking speed time (in m/s). Cross sectionally and longitudinally applied regression analyses demonstrated that the relation between comfortable and maximum walking speed does not change over time after stroke. We found that maximum speed was 1.32 times that of comfortable speed.

Table 3. Mean comfortable and maximum walking speeds, maximum to comfortable walking speed ratios and results of linear regression analysis over time.

	Post-stroke weeks																
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**	**20**	**26**	**38**	**52**
N	74	77	76	79	73	74	77	79	71	72	71	73	71	71	73	70	68
CS	.04	.15	.21	.26	.29	.37	.40	.44	.49	.53	.52	.57	.59	.62	.65	.63	.64
SD	.14	.31	.36	.41	.43	.45	.43	.45	.48	.46	.44	.45	.45	.45	.43	.41	.41
MS	.07	.21	.29	.36	.38	.48	.55	.60	.64	.71	.72	.78	.79	.80	.83	.82	.85
SD	.22	.42	.54	.59	.57	.60	.64	.64	.65	.66	.65	.66	.63	.63	.63	.57	.61
Speed ratio	1.75	1.40	1.38	1.38	1.31	1.30	1.38	1.36	1.31	1.34	1.38	1.37	1.34	1.29	1.28	1.30	1.33
b	1.36	1.25	1.44	1.43	1.32	1.27	1.42	1.38	1.30	1.39	1.41	1.44	1.35	1.35	1.33	1.35	1.44
95% CI	1.16-1.56	1.13-1.36	1.36-1.51	1.37-1.49	1.26-1.37	1.17-1.37	1.33-1.52	1.32-1.44	1.19-1.40	1.31-1.47	1.32-1.49	1.36-1.53	1.27-1.43	1.28-1.43	1.19-1.46	1.28-1.41	1.33-1.55

NOTE. All b coefficients were significant at p = .000. However, none of the added co-variables showed significance in the final prediction model. Abbreviations: CS, comfortable speed; MS, maximum speed

Furthermore, this relationship remained constant after adding the following co-variables to the linear regression model to increase its precision: patients' age, balance, hemiplegic arm and leg muscle strength and type of therapeutic intervention.
Bohannon's cross-sectional study[17] found a regression coefficient based relationship of 1.40 between comfortable and maximum walking speed in 20 subacute stroke patients. This relationship is identical to our uncorrected mean overall linear regression coefficient of 1.43, even though Bohannon measured walking speed over a 7-m distance. However, after correcting for the within-subject dependency of multiple measurements, we found an overall regression coefficient of 1.32. The validity of our findings is strengthened by the observed consistency over time and applied correction for within-subject dependency. Moreover, our findings are not affected by learning effects or measurement errors as the relationship was stable over time. This relationship may be unique for gait in hemiplegic individuals.

Our findings may have several implications. First, in a therapeutic setting maximum walking speed can be estimated with considerable accuracy by the converted comfortable walking speed. This in turn may provide the therapist with information as to the speed a stroke patient can generate to safely meet functional demands such as crossing streets or keeping pace with others who are walking. Second, this relationship remains constant irrespective of poststroke time and does not need to be corrected for age, balance, or paresis in arm or leg, nor is it affected by the type of therapeutic intervention administered. Third, the implications for gait training are important as this information allows therapists to safely train stroke patients at (1.3) higher walking speeds to better prepare them for meeting the demands imposed by independent community living. It enables therapists to measure progress and set targets for maximizing functional gait speed during the rehabilitation process. In stroke patients, speed intensive gait training induces marked speed-related improvements in body and limb kinematics and muscle activation patterns.[27]

Future research may address the nature of this apparent fixed relationship between comfortable and maximum gait speeds in age-matched healthy individuals and in subjects with other neurological disorders. It would be of particular interest to clarify the significance of the constant we observed in our study and the biomechanical and energy transformation-related mechanisms involved.

Study limitations

In our study, three comfortable walking speed measurements preceded three maximal walking speed measurements. Despite of frequent rest periods, fatigue-related speed changes may have occurred in the maximum speed measurement group. Because we adhered to our restrictive inclusion criteria, our results are based on a homogenous stroke population with no independent walking ability at onset. As a consequence, our results may not extrapolate to the stroke population at large; further investigation is required.

SUMMARY

Post-stroke maximum walking speed can be estimated with considerable accuracy by multiplying the converted comfortable walking time (in m/s) by approximately 1.3. This relationship is stable over time; It's precision does not increase when patients' age, hemiplegic arm or leg muscle strength, balance, or therapeutic intervention are considered and it is independent of time from onset.

REFERENCES

1. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: Reliability of measures of impairment and disability. Int Disabil Stud. 1990; 12: 6-9.
2. Wade DT. Measurement in neurological rehabilitation. Oxford University Press. 1992.
3. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984; 64: 35-40.
4. Wade DT, Langton Hewer R. Functional abilities after stroke: Measurement,

natural history and prognosis. J Neurol Neurosurg Psychiatry. 1987; 50: 177-82.
5. Friedman PJ, Richmond DE, Baskett JJ. A prospective trial of serial gait speed as a measure of rehabilitation in the elderly. Age and Ageing. 1988; 17: 227-35.
6. Richards CL, Malouin F, Wood-Dauphinee S, Williams JI, Bouchard JP, Brunet D. Task-specific physical therapy for optimization of gait recovery in acute stroke patients. Arch Phys Med Rehabil. 1993; 74(6): 612-20.
7. Salbach NM, Mayo NE, Wood-Dauphinee S, Hanley JA, Richards CL, Cote R. A task-orientated intervention enhances walking distance and speed in the first year post stroke: A randomized controlled trial. Clin Rehabil. 2004; 18(5): 509-19.
8. Richards CL, Malouin F, Bravo G, Dumas F, Wood-Dauphinee S. The role of technology in task-oriented training in persons with subacute stroke: A randomized controlled trial. Neurorehabil Neural Repair. 2004; 18(4): 199-211.
9. Duncan P, Studenski S, Richards L, Gollub S, Lai SM, Reker D, Perera S, Yates J, Koch V, Rigler S, Johnson D. Randomized clinical trial of therapeutic exercise in subacute stroke. Stroke. 2003; 34(9): 2173-80.
10. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004; 18(8): 833-62.
11. Mizrahi J, Susak Z, Heller L, Najenson T. Objective expression of gait improvement of hemiplegics during rehabilitation by time-distance parameters of the stride. Med Biol Eng Comput. 1982; 20: 628-34.
12. Brandstater ME, Bruin de H, Gowland C, Clarke BM. Hemiplegic gait: Analysis of temporal variables. Arch Phys Med Rehabil. 1983; 64: 583-7.
13. Wall JC, Turnbull GI. Gait asymmetries in residual hemiplegia. Arch Phys Med Rehabil. 1986; 67(8): 550-3.
14. Dettmann MA, Londer MT, Sepic SB. Relationships among walking performance, postural stability, and functional assessments of the hemiplegic patient. Am J Phys Med. 1987; 66: 77-90.
15. Friedman PJ. Gait recovery after hemiplegic stroke. Int Disabil Stud. 1990; 12: 119-22.
16. Wade DT, Wood VA, Heller A, Maggs J, Hewer RL. Walking after stroke. Scand J Rehabil Med. 1987; 19: 25-30.
17. Bohannon RW. Walking after Stroke: Comfortable versus maximum safe speed. Int J Rehabil Res. 1992; 15: 246-8.
18. Ozgirgin N, Bolukbasi N, Beyazova M, Orkun S. Kinematic gait analysis in

hemiplegic patients. Scand J Rehabil Med. 1993; 25(2): 51-5.
19. Bohannon RW. Selected determinants of ambulatory capacity in patients with hemiplegia. Clin Rehabil. 1989a; 3: 47-53.
20. Potter JM, Evans AL, Duncan G. Gait speed and activities of daily living function in geriatric patients. Arch Phys Med Rehabil. 1995; 76(11): 997-9.
21. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. Lancet. 1999; 354: 191-6.
22. Connelly DM, Stevenson TJ, Vandervoort AA. Between- and within-rater reliability of walking tests in a frail elderly population. Physiother Can. 1996; 48: 47-51.
23. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry. 1990; 53(7): 576-579.
24. Bohannon RW. Correlation of lower limb strengths and other variables with standing performance in stroke patients. Physiother Can. 1989b; 41: 198-202.
25. Kwakkel G, Wagenaar RC. Effect of duration of upper- and lower-extremity rehabilitation sessions and walking speed on recovery of interlimb coordination in hemiplegic gait. Phys Ther. 2002; 82: 432-48.
26. Twisk JWR. Applied longitudinal data analysis for epidemiology. Cambridge University Press 2003.
27. Lamontagne A, Fung J. Faster is better. Implications for speed-intensive gait training after stroke. Stroke. 2004; 35: 2543-48.

CHAPTER 4

Longitudinal robustness of variables predicting independent gait following severe middle cerebral artery stroke: A prospective cohort study

Boudewijn Kollen, Gert Kwakkel, and Eline Lindeman

Clinical Rehabilitation 2006; 20: 262-268

Abstract

OBJECTIVE:

To determine within the first 10 weeks post onset the most robust variables in the prediction of recovery of independent gait at six months post stroke.

DESIGN:

A prospective cohort study.

SUBJECTS:

One hundred and one first ever ischaemic middle cerebral artery stroke patients. None of these patients were able to walk at onset and all suffered from a marked hemiplegia.

SETTING:

Twenty four determinants, possibly related to recovery of gait at 6 months, were measured within 14 days following stroke onset. Based on Functional Ambulation Categories (FAC) independent gait was classified into present (FAC ≥ 4) or absent (FAC < 4). Bivariate logistic regression analysis was used to select determinants. Only significant determinants during the entire 10-week period were used for further weekly multivariate logistic prediction modelling of independent gait at 6 months post stroke.

RESULTS:

After six months post onset 62% (*N=63*) regained independent gait. Age, Barthel Index, Trunk Control Test, Motricity Index of arm and leg, Brunnstrom Fugl-Meyer stage of leg motor recovery, and type of intervention were significant determinants in bivariate analysis, but age of patient and Barthel Index were the most robust determinants in the final prediction model. Weekly re-evaluation produced sensitivity values between 89% and 96% and specificity values between 53% and 62%.

CONCLUSION:

In initially non-ambulatory stroke patients age and Barthel Index were the most robust variables during the first 10-week post-stroke period in the prediction of independent walking at six months. However, prediction of non-ambulation at six months proved to be less accurate.

INTRODUCTION

Evidence-based practice[1] incorporates elements of systematic monitoring of changes in functions and reliable early prediction of prognosis in stroke patients. Both aspects are paramount in stroke rehabilitation because without it no realistic goal-setting and individual prediction of recovery of gait can be attained. The expected level of walking determines to a large extent the expected level of activities of daily living and possible discharge to home.[2,3] While 70-80% of the stroke population are expected to regain the ability to walk eventually, large inter-subject differences have been found.[4-7] The results of a number of studies suggest that age[8], severity of sensory and motor dysfunction of the paretic leg[8,9], homonymous hemianopia[8,9], urinary incontinence[10], sitting balance[11], independence in ADL[11] and gait within the initial two poststroke weeks[8,11] are important factors in the prediction of the recovery of gait after six months. The true variance of the prediction models ranged from 32%[12] to 84%.[13] In particular, the poststroke timing of evaluation of determinants and outcome appeared to affect probabilities and consequently the validity of longitudinal prediction of recovery of gait. However, these studies differed in patient characteristics, included predictors, measurements as well as outcomes. Because poststroke recovery is time dependent and non-linear the identification of predictive variables not affected by the timing of poststroke prediction may facilitate conclusive clinical decision making and implementation of optimal treatment strategies.

The objective of this study was to determine the most robust variables within the initial 10 weeks in the prediction of independent walking at six months post stroke.

MATERIAL AND METHODS

Design

This prospective cohort study was part of a three-group randomized clinical trial conducted to study the effects of intensity of rehabilitation in acute middle cerebral artery stroke in 101 stroke patients. Details of design and outcome of this study are published elsewhere.[14]

Subjects

Stroke patients met the following admission criteria. Subjects (1) suffered a primary ischaemic middle cerebral artery stroke as revealed by computerized axial tomography (CAT) or magnetic resonance imaging (MRI) scan; (2) were between 30 and 80 years of age; (3) presented with an impaired motor function of the upper and lower extremities; (4) lacked a complicating medical history that may have been restrictive to performing activities of daily living; and (5) demonstrated no severe deficits in communication, memory, or understanding. Based on the Bamford Oxford Community Stroke Project classification, patients were subsequently classified in (1) total anterior circulation infarcts; (2) partial anterior circulation infarcts and; (3) lacunar anterior circulation infarcts. This classification has been found to be reliable[15,16] and valid in relation to the size of the cerebral infarct as determined by CAT-scan.[16,17] The Mini-Mental State Examination[18] was used to screen cognitive impairment and only patients with a score of ≥24 points were included in the trial. A speech therapist assessed the ability to communicate and accepted a cut-off point of the 50th percentile corrected for age on the Dutch Foundation Aphasia test.[19]

Procedure

The research protocol was implemented within 14 days after stroke onset. Final outcome was defined at 26 weeks after stroke. In addition to measuring a large number of variables described below, the line bisection task and letter cancellation task[20] were used to demonstrate the presence of visual inattention. Each entire testing procedure took 45-75 minutes depending on the level of disability. All functional measurements were performed by one independent investigator (GK).

Dependent variable

Independent gait constituted the outcome variable in this study and was based on the Functional Ambulation Categories (FAC). This test has been found to be reliable and valid in determining hemiplegic gait.[21-23] The FAC distinguishes between six ambulation levels (0 – 5) ranging from dependency to independency. A FAC score of ≥ 4 indicates independence of gait (FAC = 4) and stair climbing (FAC = 5) with or without the use of some form of assistive device. Based on these scores the FAC variable was dichotomized into unable to walk independently (FAC < 4) and able to walk independently (FAC ≥ 4).

Independent variables

Based on the results of prognostic studies[8-11] the following candidate determinants for the development of a prediction model were recorded within 14 days post stroke onset: age; Mini-Mental State Examination; Bamford Oxford Community Stroke Project classification; localization of stroke; muscle strength in upper hemiplegic extremity, balance, propriocepsis and cognition as assessed by Orpington Prognostic Scale; sensory deficit in the arm as determined by the Thumb-Finding Test; number of days following stroke onset before participation in study; muscle strength in hemiplegic extremities (Motricity Index); Trunk Control Test; Brunnstrom Fugl-Meyer motor recovery stage of hemiplegic extremities and balance and Barthel index (BI). In addition, other variables were included and tested for significance (i.e. type of intervention, sex and timed balance test).

Data analysis

Based on bivariate logistic regression analysis significant determinants were selected for the development of a multivariate logistic model for independent walking (FAC ≥ 4) at six months post stroke. A stepwise forward prediction procedure was used. All variables emerging with a significant *p*-value of ≤ 0.05 during the entire initial 10 weeks poststroke were classified as candidate determinants and selected for further modelling. The probabilities of regaining independent gait as well as the odds ratios and their 95% confidence intervals were calculated for each included determinant. SPSS classification table was used to determine sensitivity, specificity, accuracy, type I and II error and predictive value. Because the probability of regaining gait is approximately 70-80%, a table cut-off value of 0.7 has been used for testing. Each hypothesis was tested two-tailed with a $\leq$0.05 level of significance.

RESULTS

Baseline patient characteristics are presented in Table 1. Two patients died within six months after stroke as a result of a recurrent stroke or oncological comorbidity.

A statistical significant bivariate association with the FAC outcome variable during all measurements within the first 10 weeks was found for the following seven determinants: lower extremity motor recovery based on Brunnstrom Fugl-Meyer test (odds ratio (OR) ranging from 1.13 (1.06-1.22) to 1.20 (1.12-1.31)), Motricity Index of lower extremity (OR ranging from 1.03 (1.01-1.05) to 1.06 (1.03-1.09)) and upper extremity (OR ranging from 1.03 (1.01-1.05) to 1.07 (1.00-1.15)), patients' age (OR 0.93 (0.87-0.98)), Barthel Index (OR ranging from 1.44 (1.06-1.95) to 1.67 (1.33-2.10)), Trunk Control Test (OR ranging from 1.05 (1.03-1.07) to 1.09 (1.05-1.12)) and therapeutic intervention (p = 0.046). This latter variable was included after multiple categorical variables were created with reference variable. The final multivariate logistic prediction model generated only three significant variables: age during all 10 weeks, Barthel Index during eight weeks and Trunk Control Test once in the third poststroke week (Table 2). The accuracy (observed agreement) of the model ranged between 75% and 86% (Table 3). Sensitivity (defined as the proportion of true ambulatory stroke patients who were initially classified as walkers) remained consistently high (ranging from 89% to 96%) and specificity (defined as the proportion of true non-ambulatory stroke patients who were initially classified as non-walkers) moderately low (ranging from 53% to 62%) throughout the first 10 post-stroke weeks.

Table 1. Patient characteristics measured in second week after stroke.

Group	Total (±SD)
N	101
Sex (F/M)	43/58
Age, years	65.9 (10.6)
MMSE (0-30)	26.3 (2.5)
Stroke hemisphere (L/R)	42/59
Type of Stroke: (OCSP)	
TACI (0/1)	61
PACI (0/1)	33
LACI (0/1)	7
OPS (1.6-6.8)	4.3 (0.94)
Cognitive impairments: (%)	
Aphasia (0/1)	27.5
Inattention (0/1)	49.0
Visual impairments: (%)	
Hemianopia (0/1)	31.4
Visual gaze deficit (0/1)	23.5
Number of days between CVA and first intervention (±SD)	7.3 (2.8)
MI-lower extremity (0-100)	28.9 (27.4)
TCT (0/200)	54.16 (29.55)
Brunnstrom (1-6)	2.40 (1.29)
Comfortable walking speed (m/s)	0.03 (0.12)
BI (0-20)	6.15 (3.74)
FAC (0-5)	0.74 (0.96)
FAC (≥4) (0/1)	0

SD, standard deviation between brackets; *N*, number of patients; (0/1), no/yes; F/M, female/male; L/R, left/right; MMSE, Mini-Mental-State-Examination; OCSP, Oxford Community Stroke Project; TACI, total anterior circulation infarcts; PACI, partial anterior circulation infracts; LACI, lacunar anterior circulation infarcts; OPS, Orpinton Prognostic Scale; MI, Motricity Index; TCT, Trunk Control Test; Brunnstrom, Brunnstrom Score; BI, Barthel Index; FAC, Functional Ambulation Categories

Concomitant type I errors (false positives (equals one minus specificity), i.e. the proportion of true non-walkers who were initially classified as walkers) range from 37% to 47%, while type II errors (false negatives (equals one minus sensitivity), i.e. the proportion of true walkers who were initially classified as non-walkers) range from 4% to 11%.

Table 2. Significant predictive variables in final prediction model of multivariate logistic regression analysis during the initial 10 weeks post stroke in relation to independent gait (FAC ≥ 4) measured at 26 weeks post onset.

FAC versus		Weeks post stroke									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age	B	-0.15	-0.13	-0.11	-0.11	-0.10	-0.13	-0.15	-0.12	-0.11	-0.12
	p	0.05	0.01	0.02	0.01	0.03	0.02	0.01	0.02	0.03	0.03
	OR	0.86	0.88	0.90	0.90	0.90	0.88	0.86	0.89	0.90	0.89
	CI	0.75–1.00	0.80–0.97	0.83–0.98	0.83–0.98	0.83–0.99	0.79–0.98	0.77–0.96	0.80–0.98	0.82–0.99	0.80–0.99
BI	B		0.31		0.40	0.38	0.36	0.42	0.52	0.45	0.50
	p		0.03		0.00	0.00	0.00	0.00	0.00	0.00	0.00
	OR		1.37		1.49	1.46	1.43	1.53	1.68	1.57	1.65
	CI		1.04–1.79		1.20–1.86	1.19–1.79	1.16–1.78	1.20–1.94	1.27–2.23	1.24–1.98	1.29–2.13
TCT	B			0.05							
	p			0.00							
	OR			1.05							
	CI			1.02–1.08							

B, b coefficient; *p*, significance level; OR, odds ratio; CI, 95% confidence interval OR; FAC, Functional Ambulation Categories; BI, Barthel Index; TCT, Trunk Control Test

Finally, predictive values (i.e. positive predictive value is the proportion of true walkers within the group of patients initially classified as walkers and negative predictive value is the proportion of true non-walkers within the group of patients initially classified as non-walkers) ranged between 74% and 86%.

Table 3. Criterion validity in percentages for independent gait at six months post stroke.

Week	**Prior probability**	**Accuracy**	**Sensitivity**	**Specificity**	**False +**	**False -**	**PPV**	**NPV**
1	72	86	96	60	40	4	86	86
2	60	75	90	53	47	10	74	78
3	67	80	89	61	39	11	82	74
4	60	79	92	59	41	8	77	83
5	62	78	91	58	42	9	77	79
6	64	83	94	62	38	6	82	86
7	65	80	91	59	41	9	80	77
8	62	80	92	61	39	8	79	83
9	62	79	92	58	42	8	78	82
10	63	81	92	63	37	8	81	83

False + (positive) or – (negative), type I or II error; PPV, positive predictive value; NPV, negative predictive value

DISCUSSION

This is the first study to address longitudinal robustness of prediction variables based on repeated measures. This strategy was elected to identify predictive variables relative insensitive to the timing of poststroke prediction. Selection of variables was based on consistency in predicting outcome throughout the entire initial 10-week poststroke period. Bivariate logistic regression analysis produced a model that included patients' age, Motricity Index of arm and leg, Brunnstrom Fugl-Meyer of leg, Trunk Control Test, Barthel Index and type of intervention. This study demonstrates that age and Barthel Index are the most robust variables within the first 10 poststroke weeks for predicting independent walking outcome at six months (i.e. lower age and higher Barthel Index were associated with an increased probability of independent hemiplegic gait at six months). However, predicting non-ambulatory patients within the initial weeks proved to be much more difficult. This finding implies that this logistic model is better suited for predicting ambulatory patients than non-ambulatory patients.

Due to the relatively high prevalence of independent gait at six months (62%) and high sensitivity within the first 10 weeks misclassification of any real independent walkers is not likely. However, predicting independent ambulation when in fact no independent walking materializes is not inconceivable (false positive). This probability is reflected in the type I error. This presents a clinical challenge as real late non-independent walkers could be more easily missed within the prediction period due to misclassification. As a consequence the probability of false negative predictions is low.

The implications of these findings are that lower age and higher Barthel Index are the strongest predicting variables for independent gait at six months when clinical judgements over time of prediction are inconclusive. Odds ratios amount to 0.9 for age and range from 1.4 to 1.7 for Barthel Index (Table 2). In other words, each added year of age reduces the probability of regaining independent gait 0.9 times, while at the same time each higher BI point improves chances 1.4-1.7 times depending on the week of prediction. More specifically, for example in week 4 an individual of 55 years of age with a 5-point Barthel Index score has an 81%, of 60 years a 71%, of 65 years a 59% and of 70 years a 46% chance of regaining independent gait at six months. Likewise, in week 4 a 65-year-old stroke patient with a Barthel Index of 5 has a 59%, a Barthel Index of 10 a 92% and a Barthel Index of 15 a 99% probability of regaining independent gait at six months. Goal-setting and allocating rehabilitation resources can be partially based on these findings.
Acute and subacute prediction (initial 10 weeks) of stroke patients who will fail to regain independent gait at six months is less reliable. Therefore, awareness of a too optimistic estimation of walking independence at six months is required when deciding on allocating poststroke resources.

Study limitations
This study suffered from a few imperfections. First, all patients participated in a randomized controlled trial on the effects of intensive rehabilitation.[14] Although this latter study did not find any differential effects at six months it is likely that

some bias may have occurred in the time-related accuracy of prediction as a result of the systematic therapeutic interventions. Second, it is important to note that this study was restricted to a homogeneous group of patients with a first-ever severe stroke in the territory of the middle cerebral artery with a complete hemiplegia and no premorbid limitations. Predicting outcome and functional abilities using prognostic variables with regard to diagnosis[24] and functionality[25] in a relatively homogenous cohort of patients restrict external validity of developed models. Third, no validation of the developed prediction model on a second independent population took place. Therefore, external validity of this study may have suffered.

However, because none of these patients were ambulatory at onset accurate estimation of outcome becomes almost imperative because without it no realistic goal setting can be implemented in stroke rehabilitation. Therefore, future research needs to define the distinguishing early (acute and subacute) characteristics of late non-independent ambulatory stroke patients.

Clinical Messages:

- Age and Barthel index are robust and sensitive predictors for independent hemiplegic gait at six months.
- Early prediction of non-ambulatory stroke patients at six months lacks specificity.

REFERENCES

1. Duncan PW, Lai SM, Tyler D, Perera S, Reker DM, Studenski S. Evaluation of proxy responses to the Stroke Impact Scale. Stroke. 2002; 33: 2593-9
2. Wandel A, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Prediction of walking function in stroke patients with initial lower extremity paralysis: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 2000; 81: 736-738.
3. Olsen TS. Arm and leg paresis as outcome predictors in stroke rehabilitation. Stroke. 1990; 21: 247-251.

4. Chae J, Johnston M, Kim H, Zorowitz R. Admission motor impairment as a predictor of physical disability after stroke rehabilitation. Am J Phys Med Rehabil. 1995; 74: 218-223.
5. Herman B, Leyten AC, van Luijk JH, Frenken CW, Op de Coul AA, Schulte BP. Epidemiology of stroke in Tilburg, the Netherlands. The population-based stroke incidence register: 2. Incidence, initial clinical picture and medical care, and three-week case fatality. Stroke. 1982; 13: 629-634.
6. Dutch Heart Foundation. Final Report. Tilburg 1981.
7. Gresham GE, Fitzpatrick TE, Wolf PA, McNamara PM, Kannel WB, Dawber TR. Residual disability in survivors of stroke--the Framingham study. N Engl J Med. 1975; 293: 954-956.
8. Sanchez-Blanco I, Ochoa-Sangrador C, Lopez-Munain L, Izquierdo-Sanchez M, Fermoso-Garcia J. Predictive model of functional independence in stroke patients admitted to a rehabilitation programme. Clin Rehabil. 1999; 13: 464-475.
9. Patel AT, Duncan PW, Lai SM, Studenski S. The relation between impairments and functional outcomes poststroke. Arch Phys Med Rehabil. 2000; 81: 1357-1363.
10. Barer DH. Continence after stroke: Useful predictor or goal of therapy? Age and Ageing. 1989; 18: 183-191.
11. Kwakkel G, Wagenaar RC, Lankhorst GJ, Koetsier JC. Prediction models for functional recovery of ADL, walking ability and dexterity of the paretic arm after a primary ischemic middle cerebral artery stroke. In: Dynamics in functional recovery after stroke. Pons & Looijen, 1998.
12. Novack TA, Satterfield WT, Lyons K, Kolski G, Hackmeyer L, Connor M. Stroke onset and rehabilitation: time lag as a factor in treatment outcome. Arch Phys Med Rehabil. 1984; 65: 316-319.
13. Suzuki K, Imada G, Iwaya T, Handa T, Kurogo H. Determinants and predictors of the maximum walking speed during computer-assisted gait training in hemiparetic stroke patients. Arch Phys Med Rehabil. 1999; 80: 179-182.
14. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. Lancet. 1999; 354: 191-196.
15. Lindley RI, Warlow CP, Wardlaw JM, Dennis MS, Slattery J, Sandercock PA. Interobserver reliability of a clinical classification of acute cerebral infarction. Stroke. 1993; 24: 1801-1804.

16. Wardlaw JM, Dennis MS, Lindley RI, Sellar RJ, Warlow CP. The validity of a simple clinical classification of acute ischaemic stroke. J Neurol. 1996; 243: 274-279.
17. Anderson CS, Taylor BV, Hankey GJ, Stewart-Wynne EG, Jamrozik KD. Validation of a clinical classification for subtypes of acute cerebral infarction. J Neurol Neurosurg Psychiatry. 1994; 57: 1173-1179.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12: 189-198.
19. Deelman D, Liebrand W, Koning-Haanstra, Burg W van de. SAN test. An aphasia test for language comprehension and linguistic usage. Construction and standards. Lisse: Swets & Zeitlinger, 1981.
20. Lezak M. Neurophysiological assessment. New York: Oxford University Press, 1995.
21. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984; 64: 35-40.
22. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys Ther. 1986; 66: 1530-1539.
23. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. Int Disabil Stud. 1990; 12: 6-9.
24. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991; 337: 1521-1526.
25. Kalra L, Crome P. The role of prognostic scores in targeting stroke rehabilitation in elderly patients. J Am Geriatr Soc. 1993; 41: 396-400.

CHAPTER 5

Time dependency of walking classification in stroke

Boudewijn Kollen, Gert Kwakkel, and Eline Lindeman

Physical Therapy 2006; 86: 618-625

Abstract

Background and Purpose:

To facilitate optimal stroke rehabilitation, valid interpretation of observed functional recovery is required. The purpose of this study was to examine the longitudinal relationship between comfortable walking speed and Functional Ambulation Categories (FAC) scores for physically independent gait.

Subjects:

This study was a prospective cohort study with 73 subjects who were severely affected by acute stroke.

Methods:

Functional Ambulation Categories classification and walking speed were measured between weeks 4 and 26 after stroke. The responsiveness of walking speed measurements for detecting clinically important speed changes was determined, and the longitudinal association between walking speed and FAC scores and its time dependency were established. This relationship subsequently was scrutinized for possible speed changes occurring within specific FAC scores. Responsiveness ratios, random coefficient analysis, paired Student *t* tests and the Cohen Kappa statistic were used for statistical analyses.

Results:

Responsiveness ratios exceeded the smallest detectable differences. Random coefficient analysis demonstrated a significant between- and within-subject coefficient and a significant negative interaction between timing of measurements and FAC scores. Paired Student *t* tests revealed mostly significant pretest-posttest differences in walking speeds, and all Kappa values for pretest-posttest FAC scores were significant.

Discussion and Conclusion:

Walking speed measurements are sensitive for detecting clinically important changes. Functional Ambulation Categories scores are dependent on the timing of comfortable walking speed measurements after stroke. Moreover, there are indications that, in this relationship, repeated FAC appraisals are not only based on steady walking speeds, but that the walking speeds related to a specific FAC

appraisal also change and, over time, may shift gradually from higher to lower speeds.

INTRODUCTION

Stroke is the leading cause of disability among adults and frequently results in impaired mobility. Regaining the ability to walk is the goal most frequently stated by patients with hemiparesis in stroke rehabilitation.[1] The expected level of walking determines to a great extent the expected level of activities of daily living (ADL) and possible discharge to home.[2,3] However, home and community mobility presents additional challenges to walking ability, as independence requires safety of mobility.

Independent gait is considered a primary goal in stroke rehabilitation. What constitutes independent gait often is based on Functional Ambulation Categories (FAC). The FAC instrument is designed to provide information on the level of physical support needed by subjects in order to ambulate safely. This instrument has been found to be reliable and valid in classifying hemiplegic gait.[4-6]

Walking speed has been established as an important predictor of walking capability along a continuum from limited household to unlimited community ambulation.[7] Additionally, walking speed is a simple but highly reliable and responsive parameter for gait.[4,8 (page 78,79),9] Reliability has been established for test-retest and between-observer measurements.[5,10] The high correlation coefficients found for the relationship between speed measurements and time-distance parameters, such as cadence, cycle time, stance time, swing time, stride length, step length, walking velocity[11-13] as well as ambulatory performance[14-18], support the validity of speed measurement. Moreover, gait speed correlates strongly with other parameters, such as balance[19], use of walking aids[5], number of falls and ADL function in elderly people.[20]

Findings from longitudinal studies with repeated measurements over time indicate that recovery of neurological impairment and disability shows a nonlinear pattern as a function of time.[21-24] These studies also indicate that clinical determinants show considerable improvement in the early stages after stroke onset. As a consequence, differences in timing of measurement could confound predictive relationships in cross-sectional research. Therefore, information obtained from repeated measurements over time after stroke and knowledge of the stability of an instrument are required for better understanding and interpretation of observed changes.

The concept of stability of a measurement instrument is closely related to responsiveness and minimally important clinical change.[25] *Responsiveness* often is defined as the capacity of an instrument to detect a real meaningful clinical change in patient performance.[26] It consists of a signal-to-noise ratio.[27] As a consequence, increasing measurement error necessitates observing larger pretest-posttest changes. However, a single agreed-upon standard criterion of change is lacking in clinical measurement.[28] Therefore, the term "minimal clinically important difference" (MCID) was introduced.[25,27,28] Minimal clinically important differences are derived mainly from clinical judgments based on the measurement properties of an instrument, the patient population, and the magnitude of change considered "minimally important" by the practitioner.

Although repeated measurements with a simple timed walking test have been qualified as a responsive method for measuring changes in walking performance over time[9] in the general population of people with stroke, responsiveness has not been established for people with severe motor dysfunction. Therefore, the first objective in the present study was to demonstrate the adequate responsiveness of repeated walking speed measurements for detecting changes over time.

Because the effects of longitudinal measurements on the relationship between walking speed and FAC scores have not been established, the second objective of this study was to demonstrate the significance of the relationship between gait speed and independent gait capability over time. The third objective was to study the course of these walking speeds over time and to identify possible speed changes that may occur within specific FAC scores. On the basis of these objectives, the following questions were addressed in the study:

1. Are repeated comfortable walking speed measurements sensitive enough to detect poststroke changes in physically independent gait in people who are severely affected by stroke?

2. Is the relationship between FAC scores for independent gait and comfortable walking speed measurements dependent on time after stroke?
3. Are FAC appraisals subject to changing walking speeds over time after stroke?

METHOD

Design and procedures

This prospective cohort study was part of a randomized clinical trial conducted to study the effects of intensity of rehabilitation on stroke outcome. In this study, 101 subjects with stroke participated; their mean age was 65 years (SD=12.0). Subjects were included when they met the following criteria: aged 30 to 80 years; had an ischemic, first-ever, stroke involving the territory of the middle cerebral artery, as revealed by computed tomography or magnetic resonance imaging; displayed an inability to walk at first assessment; revealed no complicating medical history, such as cardiac, pulmonary, or orthopedic disorders; had no severe deficits in communication (a speech therapist assessed the ability to communicate and accepted a cutoff point of the 50th percentile corrected for age on the Dutch Foundation aphasia test[29]) or severe deficits in memory and understanding (the Mini-mental State Examination was used to assess orientation in time and place; only subjects with a score of 24 points or more were included in the trial[30]); provided written or verbal informed consent; and demonstrated sufficient motivation to participate (yes/no, at the discretion of the observer [GK]). By adhering to these inclusion criteria, we obtained a relatively homogeneous study population that initially demonstrated severe motor dysfunction. We did not find any differential treatment effects attributable to systematic therapeutic interventions at 6 months. Details about design and outcome were published elsewhere.[23] Subject characteristics at baseline are shown in Table 1.

Table 1. Subject Characteristics Measured in Week 2 After Stroke.[a]

Characteristic	Value
No. of subjects (women/men)	73 (29/44)
Age, y, $\bar{X}$ (SD)	64.8 (10.5)
MMSE score (0-30), $\bar{X}$ (SD)	26.7 (2.3)
Stroke hemisphere (left/right), no. of subjects	31/42
Type of Stroke,[b] no. of subjects	
TACI (no/yes)	36
PACI (no/yes)	30
LACI (no/yes)	7
OPS score (1.6-6.8), $\bar{X}$ (SD)	4.1 (0.92)
GCS score (0-15), $\bar{X}$ (SD)	14.8 (0.89)
Cognitive impairments (% of subjects)	
Visual inattention (no/yes)	44.4
Hemianopia (no/yes)	25.0
Visual gaze deficit (no/yes)	17.8
No. of days between CVA and first measurement, $\bar{X}$ (SD)	8.2 (2.8)
MI for lower extremity (0-100), $\bar{X}$ (SD)	35.4 (28.3)
TCT score (0/200), $\bar{X}$ (SD)	65.13 (26.26)
Brunnström score (1-6), $\bar{X}$ (SD)	2.66 (1.37)
Comfortable walking speed (m/s), $\bar{X}$ (SD)	0.04 (0.15)
BI (0-20), $\bar{X}$ (SD)	7.21 (3.46)
FAC score (0-5), $\bar{X}$ (SD)	0.94 (0.98)

[a] MMSE=Mini-Mental State Examination SD, OPS=Orpinton Prognostic Scale, GCS=Glasgow Coma Scale, CVA=cerebrovascular accident, MI=Motricity Index, TCT=Trunc Control Test, BI=Barthel Index, FAC=Functional Ambulation Categories.
[b] According to Oxford Community Stroke Project classification: TACI=Total Anterior Circulation Infarcts, LACI=Lacunar Anterior Circulation Infarcts.

Measurements

Independent gait was based on FAC measurements. This instrument distinguishes among 6 levels ranging from dependency to independency (Tab. 2). For the purpose of this study, FAC scores 3 to 5 were used because these scores do not involve physical assistance from a therapist, which could bias registered walking speed. The first measurement of gait speed was taken as soon as subjects were able to walk independently under supervision without any physical assistance from the therapist. This criterion corresponds to an FAC score of 3.[5,9] An FAC score of 4 represents unsupervised safe independence in walking on level ground, and an FAC score of 5 denotes safe ambulation anywhere, including stairs (Tab. 2). Walking devices were allowed to be used during the measurements, with the exception of a rollator or walker, because their use may bias the outcome of measurements by offering too much support to the subject. Thus, subjects who scored 0, 1 or 2 on the FAC classification or who were dependent on a rollator or walker were excluded from the analysis.

Table 2. Functional Ambulation Categories (FAC).

Score	Category	Guidance	Dichotomy
0	Nonfunctional (unable)	Person cannot walk or requires help of 2 or more people	Physical dependent gait
1	Dependent, level 2	Person requires firm, continuous support from 1 person to help with carrying weight and with balance	
2	Dependent, level 1	Person needs continuous or intermittent support from 1 person to help with balance or co-ordination	
3	Dependent on supervision	Person requires verbal supervision or stand-by help from 1 person without physical contact	Physical independent gait
4	Independent on level ground	Person can walk independently on level ground but requires help on stairs, slopes or uneven surfaces	
5	Independent	Person can walk independently anywhere	

Measurements were started within 14 days of stroke onset for all subjects, were obtained weekly up to 10 weeks, once every 2 weeks up to 20 weeks, and once at 26 weeks after onset. [23,24] All walking speed measurements were obtained by one observer (GK), and FAC scores were retrieved by the same observer either by information obtained from the therapist or, if necessary, from perusing the subject charts.[23,24] Each subject was classified for walking ability by the therapist who received instruction and training prior to the implementation of the study to ensure standardization of FAC appraisals.

Gait speed was studied at comfortable walking speeds using a standard approach for assessing gait performance.[5,16,24] In order to reduce measurement error, the mean of 3 repeated walking speed measurements was calculated.[31,24] During each session, the subjects walked 10 m at a comfortable pace. A digital stopwatch with a precision of 1/100th of a second was used for the registration of time. Between the 10-m walking tests, subjects rested for about 1 minute. Registered speed subsequently was converted to meters per second by dividing the distance walked by the time required. No encouragements were allowed to facilitate performance during a walking session.[24]

Data Analysis

We elected to conduct the statistical analysis on the data collected within the period between weeks 4 and 26 after stroke, as this represents the time window in which almost all physically independent walking change occurred in our study population. This change is required to determine the presence of time dependency of measurement.

For the first research question, the responsiveness of walking speed measurements was investigated by calculating the responsiveness ratio (RR). The RR is an effect size and is the ratio of the mean change score for subjects who clinically improved or deteriorated (ie, signal) to the variability for subjects who did not improve or deteriorate (ie, noise).[27] In order to determine improvement and deterioration in walking speed, we used an MCID of 10% as the minimal acceptable clinical change.[32,33] Therefore, the responsiveness of walking speed measurements was calculated as the ratio of the mean change score for subjects in the ≥10% scores group to the standard deviation for subjects in the group with <10% scores ($SD_{change\ group}$). In order for this measurement instrument to be responsive for detecting change over time, the signal should exceed the smallest detectable difference (or the smallest real difference) that corresponds to 1.96 times the noise level (2 times the standard deviation).

For the second research question, random coefficient analysis was used to determine the relationship between walking speed measurements and FAC scores over time and the interaction of FAC appraisals with the timing of measurements after stroke (SPSS version 12.0). This statistical method generates a within- and between- subject regression coefficient for all measurements involved by analyzing cross-sectional and longitudinal treatment and time effects simultaneously while correcting for the correlated observations

within subjects over time and allowing for regression coefficients to differ between subjects.[34] As time constitutes an independent covariate in such a regression model, this statistical method enables longitudinal analysis of unequally spaced time points of measurements. Interaction (or effect modification) occurs when the association of an independent variable (ie, FAC) with outcome (ie, comfortable walking speed) is changed by the value of a third variable (ie, time of measurement). In a multivariate regression model, interaction can be demonstrated by incorporating a product term (ie, time of measurement X FAC). A statistically significant product term indicates dependency in such a relationship; that is, the observed association between outcome and determinant is modified by the third variable.[35] Finally, in random coefficient analysis, missing data are presumed to be missing at random.
For the third research question, paired Student *t* tests were conducted to demonstrate significance in pretest-posttest differences in mean walking speeds, and Cohen Kappa statistic was used to test for agreement between FAC readings from 2 consecutive measurements after stroke (SPSS version 12.0). All hypotheses were tested in a 2-tailed fashion with a $P<.05$ level of significance.

RESULTS

The mean interval between stroke onset and first unassisted walk was 4.8 weeks (SD=2.9 weeks). None of the subjects with stroke participating in our study were able to walk unassisted during week 1 after stroke onset. At week 2, the highest level of independent gait achieved was supervised walking, and at week 3, the highest level was unsupervised walking on level ground. Because not all 101 patients from the original study[23] progressed to unassisted walking at some point in time and the number of those who did increased gradually during the time after stroke, ultimately a maximum of 73 subjects were selected for walking speed measurements. The number of subjects who were classified as physically independent walkers at any time point of measurement (with the exception of week 20) increased gradually from 25 in week 4 to 73 in week 26 (Tab. 3). The mean comfortable speed measurements ranged from 0.19 to 1.11 m/s.

Table 3. Functional Ambulation Categories (FAC) scores as Related to Mean Comfortable Walking Speeds and Number of Subjects With Stroke at Each Measurement Time Point.

FAC score		**Value at the following week after stroke:**												
		4	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**	**20**	**26**
	N	11	14	14	17	23	23	22	25	25	16	15	12	10
3		0.45	0.43	0.37	0.45	0.33	0.39	0.38	0.35	0.33	0.29	0.30	0.30	0.19
	N	12	10	9	8	12	11	11	13	15	22	23	24	23
4		0.73	0.90	0.80	0.63	0.65	0.64	0.58	0.57	0.50	0.50	0.49	0.48	0.48
	N	2	7	11	15	15	16	18	21	21	24	27	27	40
5		1.08	0.92	1.04	1.04	1.06	1.02	1.11	1.07	1.06	1.04	1.00	1.02	0.92
	N_{total}	25	31	34	40	50	50	51	59	61	62	65	63	73

N=no. of subjects

Research Question 1:

Responsiveness ratios based on a 10% MICD exceeded the smallest detectable difference and ranged from 4.36 and 17.70 (Tab. 4).

Research Question 2:

Random coefficient analysis of all poststroke measurements produced a significant between- and within- subject regression coefficient of 0.113 (Confidence Interval [CI] = 0.079 - 0.147, *P* = 0.000, count = 664) but also demonstrated a significant negative interaction between the timing of measurements and FAC scores (b = -0.003, CI = -0.005 to - 0.001, *P* = .010).

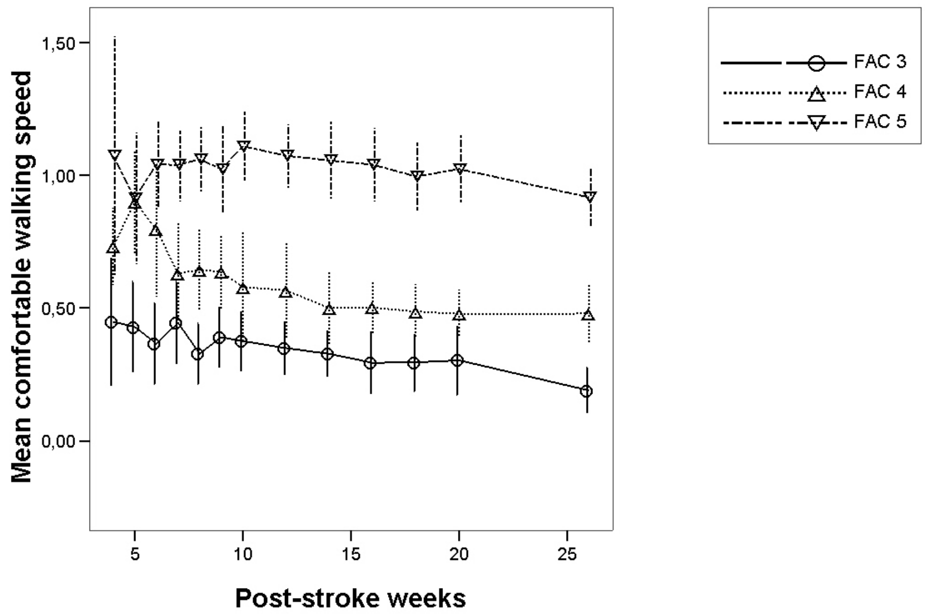
Research Question 3:

Paired Student *t* tests revealed mostly (83%) significant pretest-posttest differences in walking speeds, and Kappa values for pretest-posttest FAC scores ranged from .40 to .90 and were all significant for subsequent measurements over time after stroke (Tab. 4). The Figure shows this relationship over time along with CIs for mean walking speeds in relation to these specific FAC scores.

Table 4. Results of pretest-posttest signal-to-noise Ratios, Walking Speed Differences, and Levels of Agreement in Functional Ambulation Categories (FAC) Appraisals Between Measurements.

Parameter	**Value at the following weeks after stroke:**											
	4-5	**5-6**	**6-7**	**7-8**	**8-9**	**9-10**	**10-12**	**12-14**	**14-16**	**16-18**	**18-20**	**20-26**
Mean change score for subjects with scores of ≥10%	0.21	0.15	0.13	0.11	0.12	0.14	0.10	0.10	0.09	0.09	0.08	0.09
$SD_{change\ group}$ for subjects with scores of < 10%	0.02	0.01	0.01	0.02	0.03	0.02	0.01	0.02	0.01	0.01	0.01	0.01
Responsiveness ratio	10.21	17.70	12.24	6.69	4.36	7.17	7.28	6.45	8.83	7.68	8.33	6.49
t test for speed difference, $\bar{X}$												
d	-0.06	-0.04	-0.03	-0.03	-0.03	-0.05	-0.03	-0.03	-0.02	-0.02	-0.02	-0.02
P	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.01	0.08	0.01	0.07
Kappa value for FAC agreement												
K	0.57	0.64	0.73	0.85	0.90	0.74	0.74	0.76	0.68	0.78	0.85	0.40
P	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Figure. Mean physically independent walking speed (in meters per second) and 95% confidence intervals over time for Functional Ambulation Categories instrument scores 3, 4 and 5.



DISCUSSION

The present longitudinal study showed that comfortable walking speed measurements are sensitive enough to detect relatively minor poststroke changes in physically independent gait on the basis of FAC classification in people with a severe middle cerebral artery stroke. In addition, the results showed that the classification of walking ability on the basis of FAC scores is dependent on the timing of poststroke comfortable walking speed measurements. Moreover, there are indications that, in this relationship, repeated FAC appraisals are not only based on steady walking speeds, but that the walking speeds related to a specific FAC appraisal also change and, over time, may shift gradually from higher to lower speeds.

All RRs exceeded the smallest detectable difference in our subjects with severe stroke. In particular, within the period from weeks 4 to 7 after stroke, high RRs were observed for comfortable walking speeds, suggesting that relatively most

relevant clinical walking speed changes took place within this period. These findings indicated that walking speed measurements were sensitive for detecting clinically important changes and were suitable for demonstrating pretest-posttest time-related poststroke changes in comfortable walking speeds in our sample. Over the entire study period, a significant association was demonstrated between walking speed and FAC scores for physically independent gait. However, this relationship was dependent on the timing of measurements and became weaker as poststroke time passed (.113 minus.003 for each consecutive measurement). On the basis of paired *t* tests, pretest speeds were mostly found to be different from posttest walking speeds despite narrow measurement intervals. These differences coincided with similar pretest-posttest FAC appraisals, as the Kappa statistic agreement between FAC scores was mostly high and consistent throughout the testing period. Although FAC pretest-posttest measurements, especially those obtained weekly after stroke, were spaced closely over time and, as a result, may have been subject to recall bias, the emerging overall pattern was one of changing walking speeds coupled with highly correlated pretest-posttest FAC appraisals.
These findings suggest that repeated FAC appraisals are not only based on steady walking speeds, but that the walking speeds related to a specific FAC appraisal also change and, over time, may shift gradually from higher to lower speeds (Figure). For example, mean walking speeds related to an FAC score of 3 declined from 0.45 m/s in week 4 and 0.38 m/s in week 10 to 0.19 m/s in week 26. This observation indicates that a critical appraisal of the outcome of repeated measurements remains important, as unexpected phenomena (such as a shift) may interact with clinimetric sound (ie, reproducible, valid, and responsive) instruments and, as a consequence, may affect clinical decision making.

The underlying biological mechanism responsible for the shift in the classification of walking ability on the basis of FAC scores in our population is unknown and warrants further investigation. However, it is very likely that the therapist’s perception of safe independent walking gradually changes over time because of a developing familiarity with the walking skills of a patient. This suggests that the

therapist most familiar with a particular patient should conduct FAC appraisals for that patient. When doing so is not feasible, adequate transfer of information to the replacing therapist becomes important.
Another possible explanation is that FAC appraisals and the measurements of gait speed may not be equally sensitive to detecting time-dependent changes after stroke. Recent studies[36,37] showed that FAC-based independent gait is associated more with standing balance control, in particular generated from the non-paretic side, than it is with paresis and spasticity on the paretic side. However, gait speed is relatively more dependent on the gradual development of muscle strength and spasticity-induced stiffness on the paretic side.[38]
Finally, one may hypothesize that the use of walking devices, which usually are issued in the subacute phase to people with more severe hemiplegic strokes and with a relatively slower walking pace, affects balance control and thus FAC scores at the expense of speed.

In quality-of-life research, a similar changing relationship is observed. This phenomenon is known as *response shift*, which can be defined as a change in the meaning of a respondent's self-evaluation of a target construct as a result of a change in the respondent's internal standards of measurement ("scale recalibration" in psychometric terms), a change in the respondent's values (reprioritization), or a redefinition of the target construct (reconceptualization).[39]
The appraisal of symptoms in a longitudinal design is based on 2 assumptions. First, observers have an internalized standard of measurement for symptoms and, second, an observer's internalized standard for measurement of the dimension being used will not change over time.[40] Whereas in quality-of-life questionnaires self-report symptoms are evaluated on the basis of changes in the construct within the same person, in the present study, changes in the observer's construct were catalyzed by an objective parameter (ie, walking speed) from another person. This finding shows that changes in appraisal can be based on objective measures.
However, whether these speed changes in FAC appraisals constitute a response shift is uncertain. Response shift is a phenomenon reported as a source of

contamination of self-report measures in educational training interventions[41] and quality-of-life studies.[39] To date, such a change in the assessment of gait has not been reported. However, practitioners should be aware of a possible shift-induced bias in appraisal-related instruments. Because response shift in a placebo-controlled trial is absent in the placebo group, the outcome based on such instruments may be biased.[42] In light of response shift and appraisal, Schwartz and Rapkin called for a reconsideration of the psychometrics of quality-of-life assessments.[43]

Future research may be directed toward determining whether the mechanisms in the observed shift in FAC scores are similar to those reported in quality-of-life studies. The first step may be to implement the so-called "thentest" procedure[41] in FAC appraisals. This measure requires the observer to complete 2 posttests. The first test indicates the actual score, and the second requests a renewed judgment on the observer's pretest score. It is hypothesized that posttest and thentest measures will be based on the same internal standard of measurement and will provide an indication of the actual change that occurred. The mean difference between pretest and thentest scores indicates the magnitude and direction of the effect caused by the shift. This method also allows for the estimation of recall bias.[44]

CONCLUSION

The results of this study showed that repeated comfortable walking speed measurements are sensitive enough to detect changes in physically independent gait in people who are severely affected by stroke. Functional Ambulation Categories scores were found to be dependent on the timing of comfortable walking speed measurements after stroke. In addition, there are indications that, in this relationship, repeated FAC appraisals are not only based on steady walking speeds, but that the walking speeds related to a specific FAC appraisal change and, over time, may shift gradually from higher to lower speeds.

REFERENCES

1. Bohannon RW, Andrews AW, Smith MB. Rehabilitation goals of patients with hemiplegia. Int J Rehabil Res. 1988; 11: 181-183.
2. Wandel A, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Prediction of walking function in stroke patients with initial lower extremity paralysis: The Copenhagen Stroke Study. Arch Phys Med Rehabil. 2000; 81(6): 736-738.
3. Olsen TS. Arm and leg paresis as outcome predictors in stroke rehabilitation. Stroke. 1990; 21(2): 247-251.
4. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: Reliability of measures of impairment and disability. Int Disabil Stud. 1990; 12: 6-9.
5. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984; 64: 38-40.
6. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys Ther. 1986; 66(10): 1530-1539.
7. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke. 1995; 26: 982-989.
8. Wade DT. Measurement in neurological rehabilitation. Oxford University Press. 1992.
9. Friedman PJ, Richmond DE, Baskett JJ. A prospective trial of serial gait speed as a measure of rehabilitation in the elderly. Age and Ageing. 1988; 17: 227-38.
10. Wade DT, Langton Hewer R. Functional abilities after stroke: Measurement, natural history and prognosis. J Neurol Neurosurg Psychiatry. 1987; 50: 177-82.
11. Mizrahi J, Susak Z, Heller L, Najenson T. Objective expression of gait improvement of hemiplegics during rehabilitation by time-distance parameters of the stride. Med Biol Eng Comput. 1982; 20: 628-37.
12. Brandstater ME, Bruin de H, Gowland C, Clarke BM. Hemiplegic gait: Analysis of temporal variables. Arch Phys Med Rehabil. 1983; 64: 583-7.
13. Wall JC, Turnbull GI. Gait asymmetries in residual hemiplegia. Arch Phys Med Rehabil. 1986; 67(8): 550-3.
14. Dettmann MA, Londer MT, Sepic SB. Relationships among walking performance, postural stability, and functional assessments of the hemiplegic patient. Am J Phys Med. 1987; 66: 77-90.

15. Friedman PJ. Gait recovery after hemiplegic stroke. Int Disabil Stud. 1990; 12: 119-22.
16. Wade DT, Wood VA, Heller A, Maggs J, Hewer RL. Walking after stroke. Scand J Rehabil Med. 1987; 19: 25-30.
17. Bohannon RW. Walking after stroke: Comfortable versus maximum safe speed. Int J Rehabil Res. 1992; 15: 246-8.
18. Ozgirgin N, Bolukbasi N, Beyazova M, Orkun S. Kinematic gait analysis in hemiplegic patients. Scand J Rehabil Med. 1993; 25(2): 51-5.
19. Bohannon RW. Selected determinants of ambulatory capacity in patients with hemiplegia. Clin Rehabil. 1989a; 3: 47-53.
20. Potter JM, Evans AL, Duncan G. Gait speed and activities of daily living function in geriatric patients. Arch Phys Med Rehabil. 1995; 76(11): 997-9.
21. Skilbeck CE, Wade DT, Langton-Hewer R, Wood VA. Recovery after stroke. J. Neurol Neurosurg Psychiatry. 1983; 46: 5-8.
22. Duncan PW, Goldstein LB, Horber RD, Landsman PB, Samsa GP, Matchar DB. Similar motor recovery of upper and lower extremities after stroke. Stroke. 1994; 5: 1181-88.
23. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. Lancet. 1999; 384: 191-6.
24. Kwakkel G, Wagenaar RC. Effect of duration of upper- and lower-extremity rehabilitation sessions and walking speed on recovery of interlimb coordination in hemiplegic gait. Phys Ther. 2002: 82(5): 432-48.
25. Beckerman H, Roebroeck ME, Lankhorst GJ, Becher JG, Bezemer PD, Verbeek AL. Smallest real difference, a link between reproducibility and responsiveness. Qual Life Res. 2001; 10(7): 571-78.
26. Patten C, Kothari D, Whitney J, Lexell J, Lum PS. Reliability and responsiveness of elbow trajectory tracking in chronic post-stroke hemiparesis. J Rehabil Res Dev. 2003; 40(6): 487-500.
27. Guyatt G, Walter S, Norman G. Measuring change over time: Assessing the usefulness of evaluative instruments. J. Chronic Dis. 1987; 40(2): 171-78.
28. Stratford PW, Binkley FM, Riddle DL. Health status measures: Strategies and analytic methods for assessing change scores. Phys Ther. 1996; 76(10): 1109-23.

29. Deelman BG, Liebrand WBG, Koning-Haanstra M, van de Beug W. SAN test: An aphasia test for language comprehension and linguistic usage. In: Construction and standards. Lisse: Swets & Zeitlinger. 1981.
30. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for clinician. J Psychiatr Res 1975; 12: 189-98.
31. Connelly DM, Stevenson TJ, Vandervoort AA. Between- and within-rater reliability of walking tests in a frail elderly population. Physiother Can. 1996; 48: 47-51.
32. Lee van der J, Beckerman H, Lankhorst GJ, Bouter LM. The responsiveness of the Action research arm test and the Fugl-Meyer assessment scale in chronic stroke patients. J Rehab Med. 2001; 33: 110-113.
33. Brønfort G, Bouter LM. Responsiveness of general health status in low back pain: A comparison of the COOP charts and the SF-36. Pain. 1999; 83: 201–209.
34. Goldstein H, Browne W, Rasbash J. Multilevel modelling of medical data. Stat Med. 2002; 21: 3291-315.
35. Katz MH. Multivariable analysis. A practical guide for clinicians. Cambridge University Press. 1999.
36. Haart de M, Beelen A, Duysens J, Geurts AC. Selected posturographic parameters are associated with gait dependency in patients with postacute stroke. Arch Phys Med Rehabil. (in press).
37. Kollen BJ, Port van de I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke: A longitudinal prospective study. Stroke. 2005; 36: 2676-2680.
38. Olney SJ, Griffin MP, McBride ID. Temporal, kinematic, and kinetic variables related to gait speed in subjects with hemiplegia: A regression approach. Phys Ther. 1994; 74(9): 872-85.
39. Schwartz CE, Sprangers MAG. Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med. 1999; 48(11): 1531-1548.
40. Cronbach LJ, Furby L. How we should measure ‘change’ — or should we? Psychol Bull. 1979; 74: 68–80.
41. Howard GS, Ralph KM, Gulanick NA, Maxwell SE, Nance SW, Gerber SK. Internal invalidity in pretest-posttest self-report evaluations and a re-evaluation of retrospective pretests. Appl Psychol Measure. 1979; 3: 1–23.

42. Sprangers MAG, Van Dam FSAM, Broersen J, Lodder L, Wever L, Visser MRM, Oosterveld P, Smets EMA. Revealing response shift in longitudinal research on fatigue. The use of the thentest approach. Acta Oncologica. 1999; 38(6): 709-718.
43. Schwartz CE, Rapkin BD. Reconsidering the psychometrics of quality of life assessment in light of response shift and appraisal. Health Qual Life Outcomes. 2004; 2: 16.
44. Schwartz CE, Sprangers MAG, Carey A, Reed G. Exploring response shift in longitudinal data. Psychol Health. 2004; 19(1): 51-69.

CHAPTER 6

Predicting improvement in gait after stroke: A longitudinal prospective study

Boudewijn Kollen, Ingrid van de Port, Eline Lindeman,
Jos Twisk, and Gert Kwakkel

Stroke 2005; 36: 2676-2680

Abstract

Background and Purpose:

To study the longitudinal relationship of functional change in walking ability and change in time-dependent covariates and to develop a multivariate regression model to predict longitudinal change of walking ability.

Methods:

A total of 101 acute stroke patients with first-ever ischemic middle cerebral artery strokes was used as the population. Prospective cohort study based on 18 repeated measurements over time during the first post-stroke year. Baseline characteristics as well as longitudinal information from Functional Ambulation Categories (FAC), Fugl-Meyer leg score (FM-leg), Motricity leg score (MI-leg), letter cancellation task (LCT), Fugl-Meyer balance score (FM-balance) and timed-balance test (TBT) were obtained. Intervention consisted of a basic rehabilitation programme with additional arm, leg or air splint therapy. Main Outcome Measure constituted change scores on the Functional Ambulation Categories (FAC) over time.

Results:

In total 1532 of the 1717 change scores were available for regression analysis. The regression model showed that TBT change scores were the most important factor in predicting improvement on FAC (β=0.094; p<0.001) followed by changes scores on FM-leg (β=0.014; p<0.001), reduction in LCT omissions (β= -0.010; p<0.001) and MI leg test (β=0.001; p<0.001). In addition, time itself was significantly negatively associated with improvement (β=-0.002; p<0.001).

Conclusion:

Improvement in standing balance control is more important than improvement in leg strength or synergism to achieve improvement in walking ability, whereas reduction in visuo-spatial inattention is independently related to improvement of gait. Finally, time itself is an independent covariate that is negatively associated with change on FAC, suggesting that most pronounced improvements occur earlier after stroke.

INTRODUCTION

In the last two decades, there is growing interest in conducting longitudinal studies after stroke.[1,2,3.4] In these studies, the variables of interest are measured on the same individuals at several mostly fixed occasions. Findings from longitudinal studies with repeated measurements over time indicate that recovery of neurological impairments and disabilities shows non-linear recovery patterns over time.[3,4,5] According to Gresham, time itself appears to be one of the most important, although neglected, factors in our understanding of functional recovery after stroke.[6] To date, no study has been published that investigated the longitudinal time-dependent relationship between recovery of impairments, such as strength, synergism, visuospatial inattention and recovery of disabilities, such as gait after stroke. As a consequence, the impact of these changes as a function of time on regaining independent gait after stroke is not well understood. Moreover, knowledge about the relationship between specific impairments and limitations, such as balance control, would be useful in selecting optimal treatment strategies for improving gait after stroke.

Within the last two decades, new statistical techniques such as random coefficient modelling (multilevel modelling or hierarchical modelling) have been developed that correct for the dependency of repeated measurements within each individual.[7,8,9] The use of this technique allows for the analysis of the cross-sectional and longitudinal relationship between covariates simultaneously while taking the dependency of repeated measurements of individuals into account.[9] In standard multi-level hierarchical regression modelling, the regression coefficients presented collectively reflect the cross-sectional (ie, so called between subjects-variation) as well as the longitudinal relationship (ie, so called within-subject variation) between determinant(s) and outcome. This constitutes a limitation in the event the absolute differences between subjects exceed the changes over time. Consequently, the longitudinal within-subject relationships will be more or less overruled by the cross-sectional relationships.[10] This is likely to occur in particular when the time periods between repeated measurements are relatively short and the within-subject correlation high, which is often the case in stroke.[4,11] Because of this limitation, we elected to use a model in which the cross-sectional component is more or less 'removed' from the analysis by modelling only change scores. By modelling longitudinal change scores, one can develop a rationale for the impact of improvements of underlying functions, such as strength, synergism and balance control on changes in walking ability (ie, 'quasi-causal relationships').[10]

In the present study, we initially investigated the bivariate longitudinal relationship of improvements in walking ability and patient characteristics at baseline and improvements in impairments and functional limitations during the first year after stroke using the following time-dependent covariates: leg strength, leg synergism, visual hemi-inattention and balance control. Subsequently, we developed a multivariate multilevel regression model for the prediction of functional improvements in gait as a function of time.

MATERIALS AND METHODS

Design and procedures

This prospective cohort study was part of a randomized clinical trial conducted to study the effects of intensity of rehabilitation on stroke outcome.[4] In this study, 101 stroke patients participated with a mean age of 65 years (sd. 12,0). Patients were included when they met the following criteria: 1) they were between 30 to 80 years of age; 2) they experienced an ischemic, first-ever stroke involving the territory of the middle cerebral artery as revealed by CT- or MRI-scan; 3) they displayed an inability to walk at first assessment; 4) they revealed no complicating medical history such as cardiac, pulmonary or orthopedic disorders; 5) they had no severe deficits in communication, 6) they had no severe deficits in memory and understanding; 7) they had provided written or verbal informed consent and demonstrated sufficient motivation to participate. Details about design and outcome are published previously.[4]

Measurements

To investigate the longitudinal impact of recovery from impairments on gait, we modelled first-order change scores from 18 repeated measurements of different impairments to fit the change scores observed in walking ability.[4] All time dependent measurements were taken weekly, starting from within 14 days after stroke onset. From week 10 to week 20, biweekly measurements were obtained, whereas follow-up measurements were performed at 26, 38 of 52 weeks after stroke. All assessments were done by one observer (GK) who was blinded for treatment assignment. Walking ability was assessed with the Functional Ambulation Categories (FAC). The FAC is a reliable and valid assessment comprising of 6 categories designed to provide information on the level of physical support needed by patients to ambulate. Walking devices were allowed to be used during the measurements with the exception of a rollator or walker. Age, gender, hemisphere of stroke and social support were used as time-independent covariates and severity of paresis, stage of synergism, control for standing balance and severity of visuospatial inattention as time-dependent covariates in the multilevel regression model.

Motricity index (MI) was used to measure strength in upper extremity (UE) and lower extremity (LE). This instrument reliably assesses the presence of a paresis in stroke patients. It uses a weighted score to a maximum of 100 points for each extremity and is derived from the Medical Research Council grades. It tests 6 limb movements. Balance was measured with the timed balance test (TBT). This instrument consists of 5 components on an ordinal scale and involves timed balance (ie, 60 seconds) on progressively diminishing support surfaces. The Fugl-Meyer evaluation was used to assess motor performance. The motor section of this extensive test consists of upper limb, wrist, hand as well as lower limb ordinal scaled components. Basically, it grades the degree to which dependence on synergic movements is present. Finally, the letter cancellation task was applied to demonstrate the presence of neglect. Patients are requested to cross certain letters among many letters of the alphabet on a sheet of paper containing five lines of letters (34 per line). The difference in the number of crossed letters on the paretic and non-paretic side is scored.

Statistical analysis

The random coefficient analysis was performed with MLwiN.[12] The iterative generalized least-squares (IGLS) algorithm was used to estimate the regression coefficients.[13] Before conducting the random coefficient analysis, we calculated the change between subsequent measurements of the time-dependent covariates. These change scores were then plotted to check for compliance with model assumptions. Because time constitutes an independent covariate, random coefficient analysis enables longitudinal analysis of unequally spaced time points of measurement.

To investigate the possible longitudinal association between walking ability on FAC and covariates, initially bivariate longitudinal regression analysis was conducted with FAC change scores and time-independent covariates at baseline, such as age, gender and lateralization of stroke, as well as with t-1 change scores of the time-dependent covariates MI-leg, FM-leg, FM-balance, TBT and letter cancellation task (See Appendix, models 1 and 2). Subsequently, standardized regression coefficients were calculated, and a multivariate regression model for predicting functional recovery of gait based on FAC scores was developed (See Appendix, model 3).

The likelihood ratio test was used to evaluate the necessity for allowing random regression coefficients into the model, whereas the Wald-test was used to obtain a *p*-value for a particular regression coefficient.[10] For all tests, a two-tailed significance level of .05 was used.

RESULTS

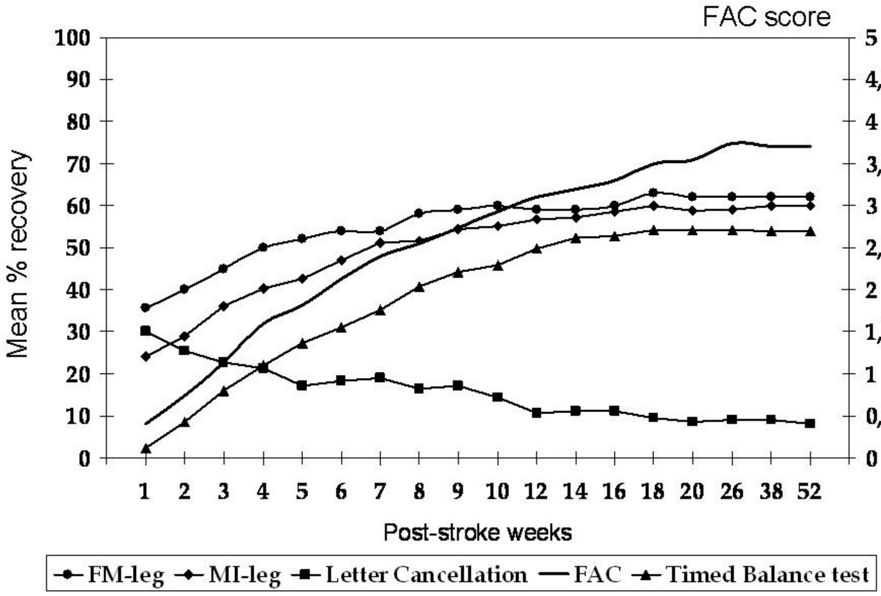
Patient characteristics of all 101 stroke patients are presented in Table 1. None of the stroke patients participating in our study was able to walk unassisted during first week after stroke onset. Mean recovery profiles for MI leg, FM leg, FM balance, letter cancellation task and TBT for all 18 measurements are illustrated in the Figure. In total, 1530 of the 1717 change scores were available for modelling. All change scores were normally distributed based on visual plotting.

Table 1. Patient characteristics.

Group	Total
N	101
Gender (F/M)	43/58
Age, years (±SD)	65.4 (10.5)
MMSE (±SD)	26.4 (2.5)
Hemisphere of Stroke (L/R)	41/61
Type of Stroke: (OCSP)	
-TACI	55
-PACI	33
-LACI	14
OPS (±SD)	4.4 (0.8)
GCS (±SD)	14.8 (0.8)
Cognitive disturbances: (%)	
-aphasia (0/1)†	27.5
-inattention (0/1)	49.0
Impairments of vision: (%)	
-hemianopia (0/1)	31.4
-visual gaze deficit (0/1)	23.5
Days between stroke-onset and first assessment (±SD)	7.3 (2.8)
MI-arm(±SD)	13.5 (23.3)
MI-leg(±SD)	21.7 (24.4)
sitting balance (0/1)	26/76
BI (%) (±SD)	28.5 (17.2)
FAC score (±SD)	0.8 (1.0)
ARA score (±SD)	3.9 (9.7)
Risk factors: (%)	
-hypertension (160/95) (0/1)	45.1
-smoking habit (0/1)	36.3
-family hereditary (0/1)	31.3
-cardiac disease (0/1)	28.4
-diabetes mellitus (0/1)	14.7
-hyperlipedemia (0/1)	9.8

N, Number of patients; SD, standard deviation in brackets; (0/1)=no/yes; F/M, Female/Male; MMSE, Mini-Mental State Examination (range 0-30); L/R, Left/Right; OCSP, Oxford Community Stroke Project; TACI, Total Anterior Circulation Infarcts; PACI, Partial Anterior Circulation Infarcts; LACI, Lacunar Anterior Circulation Infarcts; OPS, Orpington Prognostic Score (range 1.6-6.8); GCS, Glasgow Coma Scale (range 0-15); † =Based on the Dutch Foundation Aphasia test (ie, SAN); MI, Motricity Index (range 0-200); BI, Barthel Index (range 0-100); FAC, Functional Ambulation Categories (range 0-5); ARA, Action Research Arm test (range 0-57)

Figure. Mean normalized recovery patterns (% of maximum attainable recovery) for impairments as a function of time (N=101; Left Y-axis). Mean recovery patterns (raw change scores) for Functional Ambulation Categories (FAC) (right Y-axis) (FM-leg, Fugl-Meyer leg; MI-leg, Motricity Index leg).



Bivariate random coefficient analysis of change scores

Table 2 shows the bivariate regression coefficients, their errors, and significance for time-independent covariates and change scores of time-dependent covariates. Except for age (p = 0.046) none of the time-independent covariates was significantly associated with the change scores of FAC. However, all time-dependent covariates were statistically significantly associated with the change scores on FAC. The highest regression coefficient was observed for improvements on the TBT followed by the FM balance score, FM-leg, LCT, time and MI-leg score. Time after onset and LCT showed to be negatively associated with change on FAC.

Table 2. Bivariate regression coefficients with random and fixed slopes (β standard errors in parenthesis) for time-independent and time-dependent covariates for recovery of gait during the first year after stroke.

	N=101		
Determinant	**β value (β-error)**		***p*-value**
Time-independent covariates:	*Fixed slope*		
Gender (M/F)	0.010 (0.025)		0.69
Age (range: 30-80)	-0.002 (0.001)		0.05*
Hemisphere of stroke (L/R)	-0.006 (0.025)		0.81
Type of stroke (OCSP)	-0.023 (0.020)		0.25
Days between stroke-onset and first assessment	-0.002 (0.004)		0.62
MMSE	0.008 (0.005)		0.11
visual gaze deficit (0/1)	-0.011 (0.029)		0.70
homonymous hemianopia (0/1)	-0.018 (0.027)		0.51
baseline visual inattention (0/1)	-0.027 (0.025)		0.28
baseline TFT score (0-3)	-0.014 (0.013)		0.28
baseline OPS (1.6-6.8)	0.013 (0.013)		0.32
baseline sitting balance (0/1)	0.050 (0.028)		0.07
urinary incontinence (0/1)	-0.013 (0.025)		0.60
baseline MI-leg	0.000 (0.000)		-
baseline FM-leg	0.001 (0.002)		0.62
baseline TCT	0.001 (0.000)		0.32
baseline FM-balance	0.008 (0.005)		0.11
baseline TBT	0.007 (0.015)		0.64
baseline FAC	0.007 (0.013)		0.59
baseline BI	0.004 (0.003)		0.18
social support (0/1)	-0.021 (0.026)		0.42
Time-dependent covariates:	*Fixed slope*	*Random slope*	
Δ MI leg	-	0.014 (0.002)	0.00***
Δ FM-leg	0.053 (0.005)	-	0.00***
Δ FM-balance	-	0.091 (0.015)	0.00***
Δ LCT	-	-0.025 (0.007)	0.00***
Δ TBT	0.116 (0.019)	-	0.00***
Time of measurement post-stroke	-0.018 (0.003)	-	0.00***

**p*<0.05; ***p*<0.01; ****p*<0.001; (0/1)=no/yes; Δ = change score of 1 time lag (ie, from t to t-1); N, Number of patients; β value = regression coefficient; MMSE, Mini-Mental State Examination (range 23-30); TFT, Thumb Finding Test (range 0-3); OPS, Orpington Prognostic Score (range 1.6-6.8); TBT, Timed Balance Test (range 1-5); MI-leg, Motricity Index leg score (range 0-100); FM-leg, Fugl-Meyer leg score (range 0-34); FM-balance, Fugl-Meyer balance score (range 0-34); LCT, Letter cancellation task score

Multivariate random coefficient modelling of significant time-dependent covariates

Table 3 presents the significant covariates of the multivariate random coefficient model. This model includes change scores of the covariates TBT, FM-leg, LCT, MI leg as well as time itself. This model predicted 18% of the variance of outcome on change of FAC.

Table 3. Multivariate regression model for progress of walking ability during the first year after stroke.

	N=101		
Fixed effect	**standardized β coefficient**	**SE**	***p*-value**
Intercept	0.215	0.029	<0.00***
Δ TBT	0.094	0.019	0.00**
Δ FM-leg	0.014	0.005	<0.00***
Δ LCT	-0.010	0.006	0.00**
Time	-0.002	0.003	0.01**
Δ MI-leg	0.001	0.002	<0.00***

*$p<0.05$; **$p<0.01$; ***$p<0.001$; Δ = change score of 1 time lag (ie, from t to t-1); N, Number of patients; β value = regression coefficient; se, standard error; TBT, Timed Balance Test; FM-leg, Fugl-Meyer leg score (range 0-34); LCT, Letter Cancellation Task (range 0-20); MI-leg, Motricity Index leg score (range 0-100)

DISCUSSION

To the best of our knowledge, this is the first longitudinal study that investigated the functional impact of observed changes of time-dependent covariates such as balance[14], synergism[15], leg strength[16], visuo-spatial inattention[17,18] and time[3], on the recovery of gait after acute stroke. The significant bivariate random coefficients found in the present study confirm the assumption that larger improvements in impairments and gait-related functional limitations, including control of standing balance, are highly associated with improvements in gait. The present study further shows that improvement in standing balance, as measured with the timed-balance test or FM balance test, is the most important determinant for regaining gait based on the functional ambulation categories, whereas changes in synergism and muscle strength of the paretic leg are less associated with recovery of walking ability. This finding is in agreement with the literature suggesting that recovery in postural control of standing is more important for regaining gait than the restoration of support functions and voluntary control of the paretic leg itself. This finding also suggests that the use of compensatory strategies in the standing position, e.g. shifting the weight to the non-paretic side, is more important than muscle strength in the lower paretic limb for regaining gait.[19,14,20]

Interestingly, the present findings also show that visuospatial inattention was weakly but significantly and negatively related to recovery of gait, suggesting that more reductions in visuospatial inattention, as expressed by the difference in the number of omissions in the LCT, are associated with better improvements in gait. This latter finding is in agreement with the studies that show that patients with visuo-spatial neglect experience more difficulty in negotiating obstacles[21] and walking appropriate trajectories than controls.[18]

Finally, time itself is an independent fixed determinant in the multivariate model which is significantly negatively associated with recovery of gait, suggesting that most improvements take place sooner after stroke. This finding is in agreement with the general assumption about the speed of neurological (and with that, functional) recovery after stroke (ie, the largest improvements are observed early after stroke onset and these changes subsequently gradually level off).[22,6,3]

However, in part, gradual smaller change scores over time may have been the result of the availability of a reduced range for changes (ceiling effect).

The major advantage of a repeated measurement design as compared to a traditional prognostic design is that it represents reality far better than just two measurements over time. Instead of observing two images of the patients' functional status frozen in time, it becomes feasible to analyze several closely sequential images over time, providing insight into the dynamics of recovery. This, in turn, allows for a more valid interpretation of the factors that modulate the process of spontaneous neurological recovery.

More research is needed for the development of prognostic models based on the within-subject variability of covariates as a function of time for the accuracy of functional change. To understand the impact of time post-stroke on recovery, future research should focus on the impact of individual neurological changes of impairments on functional recovery and the significance of using compensatory strategies to improve gait.[3,23,20,14] This information can than be used to determine the relationship between recovery of impairments and disabilities, such as gait.[3] Recovery of disabilities reflects the intrinsic recovery of impairments as well as applied compensation.[3] Understanding the different mechanisms involved as well as the optimal time windows for functional recovery allows clinicians to develop treatment programmes that are more effective in maximizing underlying mechanisms responsible for neurological and adaptive (ie, compensatory) recovery.[3,24,5]

The relatively low regression coefficients observed for the covariates and the low explained variance of about 18% for included determinants suggests that most progress cannot be explained by restitution of function. Most likely this progress is facilitated by the use of compensation strategies that involve the participation and adaptation of the non-paretic side to enable gait. This latter finding suggests that recovery after stroke occurs to a large extent through behavioral compensation, rather than via processes of "true recovery" alone.[5] Future studies may explore the relationship between observed behavioral adaptations and improved skills after stroke by addressing the issue of which changes in motor control coincide with functional improvements. This knowledge may contribute to determining the best way to subject stroke patients to therapeutic exercises. Finally, modelling change scores in a repeated measurement design (whereby the measures are nested within the subjects) offers also opportunities for the exploration of the longitudinal relationship between, on the one hand, macroscopic neuroplastic changes observed (e.g. fMRI and TMS), and, on the other hand, found changes in neurological and kinematical examination.

Appendix

For the bivariate longitudinal regression analysis of time-dependent variables, we used the following regression model:

$$(\mathbf{Y_{it} - Y_{it-1}) = \boldsymbol{\beta}_{0it} + \Sigma\boldsymbol{\beta}_{1j}\, (X_{ijt} - X_{ijt-1}) + \boldsymbol{\varepsilon}_{it}} \quad \textbf{(model 1)}$$

Where Y_{it} are the observations for subject I at time t and Y_{it-1} the observations for subject I at time t-1, reflecting the change score for the dependent variable 'walking ability' based on FAC registration. Regression coefficient β_{0it} reflects the random intercept and β_{1j} the random selected regression coefficient for the time-dependent covariate j and X_{ijt} the time-dependent variable j for subject I at time t and X_{ijt-1} at time t-1.

For the bivariate longitudinal regression analysis of time-independent variables, we used the following model:

$$(\mathbf{Y_{it} - Y_{it-1}) = \boldsymbol{\beta}_{0it} + \Sigma\boldsymbol{\beta}_{1m}\, X_{im} + \boldsymbol{\varepsilon}_{it}} \quad \textbf{(model 2)}$$

Where Y_{it} are the observations for subject I at time t and Y_{it-1} the observations for subject I at time t-1, reflecting the change score for the dependent variable "walking ability" measured with the FAC. Regression coefficient β_{0it} is a random intercept and β_{1m} the regression coefficient of the time-independent covariate m and X_{im} the time-independent covariate for subject I. ε_{it} represents the error for subject I at time t.

To develop a multivariate regression model for predicting functional recovery of gait based on FAC scores, the following statistical model was used:

$$(\mathbf{Y_{it} - Y_{it-1}) = \boldsymbol{\beta}_{0it} + \Sigma\boldsymbol{\beta}_{1j}\, (X_{ijt} - X_{ijt-1}) + \boldsymbol{\beta}_{2}t + \Sigma\boldsymbol{\beta}_{3m}\, X_{im} + \boldsymbol{\varepsilon}_{it}} \quad \textbf{(model 3)}$$

Where Y_{it} are the observations for subject I at time t and Y_{it-1} the observations for subject I at time t-1, reflecting the change scores for the dependent variable 'walking ability' measured with the FAC. Regression coefficient β_{0it} is a random intercept and β_{1j} the random selected regression coefficient for time-dependent variable j and X_{ijt} the time-dependent variable j for subject I at time t and X_{ijt-1} at time t-1. β_2 is the regression coefficient for time t and β_{3m} the regression coefficient for time-independent covariate m and X_{im} the time-independent covariate. Finally, ε_{it} represents the error for subject I at time t.

REFERENCES

1. Friedman PJ, Richmond DE, Baskett JJ. A prospective trial of serial gait speed as a measure of rehabilitation in the elderly. Age and Ageing. 1988; 17: 227-35.
2. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen stroke study. Arch Phys Med Rehabil. 1995; 76: 27-32.
3. Duncan PW, Goldstein LB, Horner RD, Landsman PB, Samsa GP, Matchar DB. Similar motor recovery of upper and lower extremities after stroke. Stroke. 1994; 25: 1181-8.
4. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. Lancet. 1999; 354 (9174): 191-6.
5. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: Facts and theories. Restor Neurol Neurosci. 2004; 22: 281-99.
6. Gresham GE. Stroke outcome research. Stroke 1986; 17: 358-362.
7. Zeger SL, Liang K-Y. An overview of methods for the analysis of longitudinal data. Stat Med. 1992; 11: 1825–1839.
8. Diggle PJ, Liang K-Y, Zeger SL. Analysis of longitudinal data. New York: Oxford University Press Inc. 1994.
9. Goldstein H, Browne W, Rasbash J. Multilevel modelling of medical data. Stat Med. 2002; 21: 3291-315.
10. Twisk JWR. Applied longitudinal data analysis for epidemiology. Cambridge University Press. 2003.
11. Goodwin N, Sunderland A. Intensive, time-series measurement of upper limb recovery in the subacute phase following stroke. Clin Rehabil. 2003; 17: 69-82.
12. Rashbash J, Browne W, Goldstein H, et al. A user’s guide to MLwiN. London: Centre for Multilevel Modelling. 2000.
13. Snijders TAB, Bosker RJ. Multilevel Analysis. An introduction to basic and advanced multilevel modeling. London, Thousand Oaks CA, New Delhi: Sage Publications Ltd. 1999.
14. De Haart M, Geurts AC, Huidekoper SC, Fasotti L, van Limbeek J. Recovery of standing balance in postacute stroke patients: A rehabilitation cohort study. Arch Phys Med Rehabil. 2004; 85: 886-95.

15. Brandstater ME, Bruin de H, Gowland C, Clarke BM. Hemiplegic gait: Analysis of temporal variables. Arch Phys Med Rehabil. 1983; 64: 583-7.
16. Wade DT, Langton Hewer R. Functional abilities after stroke: Measurement, natural history and prognosis. J Neurol Neurosurg Psychiatry. 1987; 50: 177-82.
17. Friedman PJ. Spatial neglect in acute stroke: The line bisection test. Scand J Rehabil Med. 1990; 22: 101-6.
18. Berti A, Smania N, Rabuffetti M, Ferrarin M, Spinazzola L, D'Amico A, Ongaro, E, Allport A. Coding of far and near space during walking in neglect patients. Neuropsychology. 2002; 16: 390-9.
19. Dettmann MA, Londer MT, Sepic SB. Relationships among walking performance, postural stability, and functional assessments of the hemiplegic patient. Am J Phys Med. 1987; 66: 77-90.
20. Garland SJ, Willems DA, Ivanova TD, Miller KJ. Recovery of standing balance and functional mobility after stroke. Arch Phys Med Rehabil. 2003; 84: 1753-9.
21. Said CM, Goldie PA, Patla AE, Sparrow WA, Martin KE. Obstacle crossing in subjects with stroke. Arch Phys Med Rehabil. 1999; 80: 1054-9.
22. Newman M. The process of recovery after hemiplegia. Stroke. 1972; 3: 702-10.
23. Kwakkel G, Wagenaar RC. Effect of duration of upper- and lower-extremity rehabilitation sessions and walking speed on recovery of interlimb coordination in hemiplegic gait. Phys Ther. 2002; 82: 432-48.
24. Dombovy ML. Understanding stroke recovery and rehabilitation: Current and emerging approaches. Curr Neurol Neurosci Rep. 2004; 4: 31-5.

CHAPTER 7

Effects of overloading of the lower hemiparetic extremity on walking speed in chronic stroke patients: A pilot study

Boudewijn Kollen, Marc Rietberg, Gert Kwakkel, and Kees Emmelot

NeuroRehabilitation 2000; 14: 159-164

Abstract

The objective of this pilot study was to investigate the carryover effects on comfortable walking speed after overloading the lower hemiparetic extremity in chronic stroke patients. A single subject research study was conducted using a withdrawal design (A-B-A-B-A) on three patients with ischemic middle cerebral artery infarction. Chronic stroke patients were recruited with stage 3 or 4 Fugl-Meyer scores in the lower extremity and the ability to ambulate independently without walking aids. Based on this withdrawal design, the daily procedure included walking at comfortable speeds 5 × 10 meters during the A1 phase and 3 × 10 meters during all subsequent phases. This procedure was repeated for five consecutive days. Two lbs (B_1) and 6 lbs (B_2) weight cuffs were attached to the distal lower hemiparetic extremity and randomized over the two B phases. Control (A_1, A_2, A_3) and intervention (B_1, B_2) phases were alternated with brief resting periods. Mean comfortable walking speed for 10 meters constituted the outcome variable. All patients showed significant differences between phases ($\chi^2 = 34.187$; $p < 0.001$). However, with the exception of a carry-over effect between the A_1 (0.86 m/sec) and A_2 (0.89 m/sec) phases in one subject ($p = 0.043$) no significant carry-over effects were found on ensuing A_2 and A_3 control phases. Although gradual improvements in comfortable walking speed between subsequent days were found the present pilot study did not demonstrate favourable group effects on comfortable walking speed as a result of limb overloading.

INTRODUCTION

Regaining the ability to walk is the most frequently stated goal by hemiparetic stroke patients in rehabilitation.[1] Stroke rehabilitation offers many treatment strategies to achieve this goal. However, one popular strategy (Bobath approach) predominates current practice.[2,3] This concept is based on the perception that muscle weakness and spasticity are linked in that weakness in the agonist is attributable to spastic restraint imposed by the antagonistic muscle group.[4] Therefore, Bobath proposed that the normalization of muscle tone is a priority in treatment. Muscle strengthening is avoided because of its concomitant adverse effects on spasticity. Strengthening weak and unresponsive muscles would only increase co-contraction and reduce coordination. However, recent evidence does not support a major role for the spasticity of the antagonist in limiting voluntary activation of the agonist. Studies indicate that muscle weakness is not caused by exaggerated co-contractions of dominant spastic antagonists, but is the result of inadequate recruitment of agonists.[5,6,7,8,9] Moreover, findings suggest that spasticity does not increase with training of synergies or strengthening of paretic muscles nor does muscle strengthening cause any detrimental effects.[5,10,11,8,12,13] Several studies show that strength training can be beneficial to patients in stroke rehabilitation.[14,15,16,17,18,12,13,19] Some stroke patients experience a disproportional heaviness in their hemiplegic lower extremity during gait. This may be due to their inability to actively hold and move the weight of the leg. However, the inability to sense adequate gradation of effort may add to this problem.[20,21,22] Moreover, sensory disturbances and attentional disorders may also contribute to dysfunction and perceived sensation. Therapeutic intervention may incorporate elements directed to intensify sensation and strengthen paretic muscles. In an attempt to achieve these treatment goals, we temporarily overloaded the hemiplegic lower extremity with a weight cuff in chronic stroke subjects. It was hypothesized that overloading the hemiparetic extremity would generate increased motor output resulting in carry-over effects.* In some sports these effects are commonly used in order to improve performance. For instance, before batting baseball players practice with a weighted bat to facilitate swinging.

Analogous to principles derived from sports training procedures, the objective of this pilot study was to investigate carryover effects of overloading of the lower hemiparetic extremity on comfortable walking speed in stroke patients. Such overloading, induced carry-over effects would be beneficial and desirable in therapy. If these effects occur then overloading would constitute an advantageous effective adjunct to regular therapeutic interventions in stroke rehabilitation.

* Carry-over from the effect of treatments in preceding phases on ensuing phases.

METHOD

Patient selection

Three chronic stroke patients were recruited with stage 3 or 4 Fugl-Meyer scores in the lower extremity and the ability to ambulate independently without walking aids for five minutes (Table 1). In addition, the included patients were oriented and able to communicate adequately. Informed consent was obtained.

Table 1. Characteristics of participating patients.

Subject	Gender	Age	Months post-stroke	Hemiplegia	FM motor score LE
A	male	46	40	Right	stage 3
B	male	61	36	Left	stage 3
C	female	70	54	Left	stage 4

FM, Fugl-Meyer; LE, lower extremity

Study design

A single subject research study was conducted using a withdrawal design (A-B-A-B-A)[23] on three patients with primary ischemic middle cerebral artery infarction. This withdrawal design incorporated the following phases:

A_1 : Electronic registration with a TAG Heuer SA system of comfortable walking speed during 5 times 10 meters.

B_1 : Application of 2 lbs weight cuff to the distal paretic lower extremity (on and just above the ankle). Next electronic registration with a TAG Heuer SA system of comfortable walking speed during 3 times 10 meters.

A_2 : Removal of weight cuff followed by electronic registration with a TAG Heuer SA system of comfortable walking speed during 3 times 10 meters.

B_2 : Application of 6 lbs weight cuff to the distal paretic lower extremity (on and just above the ankle). Next electronic registration with a TAG Heuer SA system of comfortable walking speed during 3 times 10 meters.

A_3 : Removal of weight cuff followed by electronic registration with a TAG Heuer SA system of comfortable walking speed during 3 times 10 meters.

Phases B_1 and B_2 were randomized by tossing a coin. Between phases A_1 – B_1 or B_2 and A_2 or A_3 – B_2 or B_1, 2 minutes of rest provided the sitting patient with an adequate wash-out period and reduced possible fatigue effects on walking performance. In addition, 15 seconds of idle standing position was introduced between phases B_1 – A_2 and B_2 – A_3 and between each gait cycle of 10 meters. Patients were instructed to walk at their comfortable speeds over the marked course of 10 meters starting from idle position. They were asked to wear the same shoes during the course of the study. Based on this withdrawal design, the daily procedure included walking at comfortable speeds over 5 times 10 meters during the A1 phase and 3 times 10 meters during all subsequent phases. This procedure was repeated for five consecutive days at the same time of day. Two lbs (B_1) and 6 lbs (B_2) weight cuffs were randomized over the two B phases to determine the sequence of weighting (A_1, B_1, A_2, B_2, A_3 or A_1, B_2, A_3, B_1, A_2). Mean comfortable walking speed recorded in seconds over 10 meters and converted to meters per second (m/sec) constituted the outcome variable. During the course of this study, none of the participating patients received any additional physiotherapeutic intervention. However, prior to this study, one patient was provided with 30 minutes of regular physiotherapy each week in an attempt to maintain her present slightly declining level of ADL functioning.

Measurements

Fugl-Meyer motor evaluation[24] was used for patient selection. It's reliability and validity have been previously demonstrated.[25,26,27,28,29] A TAG Heuer SA system was used for electronic time registration of walking speed over a marked walking course of 10 meters. Just prior to walking in the B phases, 2 lbs and 6 lbs weight cuffs (Rolyan - Smith & Nephew®) were attached with Velcro to the appropriate hemiparetic extremity.

Statistics

In order to demonstrate possible overloading-induced effects on walking speed, Friedman one-way ANOVA by ranks was conducted on mean comfortable walking speed variable in all phases. When significant differences were found between phases or days, a post hoc Wilcoxon Matched-Pairs Signed-Ranks test was performed to identify the phase or day that differed significantly from the others. Each hypothesis was tested two-tailed with $p < 0.05$ as the significance level.

RESULTS

Mean walking velocities during ensuing phases for individual subjects as well as for subjects collectively are depicted in Table 2. As a group patients showed significant differences in mean walking speed between phases ($\chi^2 = 34.187$; $p < 0.001$). Post hoc analysis demonstrated a significant decrement on comfortable walking speed during the B_1 and B_2 phases when compared to the A_1 phase, whereas no significant differences were found among mutual A phases. In addition, walking speed decreased significantly ($p = 0.005$) as overloading increased during the B_1 phase from 0.80 to 0.77 m/sec and B_2 phase from 0.80 to 0.73 m/sec (Table 2).

No significant carry-over effects were found on ensuing A_2 and A_3 control phases. However, at an individual subject level, significant differences occurred between the A_2 (0.84 m/sec) and A_3 (0.82 m/sec) phases in subject A ($p = 0.043$) and between the A_1 (0.86 m/sec) and A_2 (0.89 m/sec) phases in subject B ($p = 0.043$) (Table 3).

Table 2. Mean comfortable walking speed in meters per second. Phases (A_1, A_2, A_3, B_1 and B_2) and subsequent days (D_1, D_2, D_3, D_4 and D_5) are shown.

	Phases					**Days**				
	A_1 Mean Sd	**A_2** Mean Sd	**A_3** Mean Sd	**B_1** Mean Sd	**B_2** Mean Sd	**D_1** Mean Sd	**D_2** Mean Sd	**D_3** Mean Sd	**D_4** Mean Sd	**D_5** Mean Sd
Subject A	0.85	0.84	0.82	0.81	0.76	0.80	0.80	0.83	0.80	0.85
	0.03	0.04	0.04	0.02	0.04	0.05	0.03	0.04	0.04	0.04
Subject B	0.86	0.89	0.89	0.85	0.80	0.81	0.86	0.83	0.89	0.90
	0.04	0.05	0.03	0.03	0.06	0.06	0.06	0.03	0.03	0.04
Subject C	0.69	0.70	0.69	0.65	0.63	0.70	0.67	0.66	0.65	0.67
	0.03	0.04	0.03	0.04	0.04	0.04	0.06	0.04	0.04	0.03
A + B + C	0.80	0.81	0.80	0.77	0.73	0.77	0.77	0.77	0.78	0.81
	0.09	0.09	0.09	0.09	0.09	0.07	0.10	0.09	0.11	0.11

Sd, standard deviation

Table 3. Results of nonparametric testing. Only significant differences are shown.

	Phases		**Days**	
	Friedman	Wilcoxon (m/sec)	Friedman	Wilcoxon (m/sec)
Subject A	$p = 0.012$	0.85–0.76 ($A_1 > B_2$)	$p = 0.034$	0.80–0.85 ($D_2 < D_5$)
		0.84–0.82 ($A_2 > A_3$)		0.83–0.80 ($D_3 > D_4$)
		0.84–0.81 ($A_2 > B_1$)		0.80–0.85 ($D_4 < D_5$)
		0.84–0.76 ($A_2 > B_2$)		
		0.81–0.76 ($B_1 > B_2$)		
Subject B	$p = 0.006$	0.86–0.89 ($A_1 < A_2$)	$p = 0.002$	0.81–0.86 ($D_1 < D_2$)
		0.86–0.80 ($A_1 > B_2$)		0.81–0.89 ($D_1 < D_4$)
		0.89–0.85 ($A_2 > B_1$)		0.81–0.90 (D1 < D_5)
		0.89–0.80 ($A_2 > B_2$)		0.86–0.89 ($D_2 < D_4$)
				0.86–0.90 ($D_2 < D_5$)
				0.83–0.89 ($D_3 < D_4$)
				0.83–0.90 ($D_3 < D_5$)
Subject C	$p = 0.034$	0.70–0.65 ($A_2 > B_1$)	$p = 0.345$	–
		0.70–0.63 ($A_2 > B_2$)		
A + B + C	$p < 0.001$	0.80–0.77 ($A_1 > B_1$)	$p = 0.038$	0.77–0.81 ($D_2 < D_5$)
		0.80–0.73 ($A_1 > B_2$)		0.77–0.81 ($D_3 < D_5$)
		0.81–0.77 ($A_2 > B_1$)		
		0.81–0.73 ($A_2 > B_2$)		0.78–0.81 ($D_4 < D_5$)
		0.77–0.73 ($B_1 > B_2$)		

>, Faster walking speed in meters per second (m/sec); <, slower walking speed in meters per second (m/sec)

Only subject B demonstrated a significant carry-over effect due to limb overloading. Finally, collectively these patients showed significant differences in mean walking speed between subsequent days (χ^2 = 10.133; p = 0.038) (Table 3). Post hoc analysis demonstrated significantly higher walking speeds on Day 5 when compared to Days 2, 3 and 4 (Table 2).

DISCUSSION

This pilot study did not demonstrate limb-overloading induced carry-over group effects on ensuing control phases. At a subject level only one patient showed a significant carry-over effect between the A_1 and A_2 phases. Moreover, although gradual improvements in comfortable walking speed between subsequent days were found, this pilot study did not demonstrate favourable group effects on comfortable walking speed as a result of limb overloading. These gradual improvements on Day 5 when compared to Days 2, 3 and 4 may have been caused by confounders, such as learning. Walking speed is considered to be an effective indicator of the degree of abnormality in hemiplegic gait.[30] In the stroke population, walking speed is correlated to balance, degree of lower limb strength recovery, Barthel Index score, cadence of gait, degree of ambulatory independence and rating of overall gait appearance.[31,32,33,26,27,30,34,35,36] Comfortable walking speed is a commonly used measure in clinical settings.[18] It can be measured using the 10 meters timed walking test, which is found relevant, reliable, valid, responsive to change and easy to measure.[37,38] Overloading is used as a strength training procedure in sports[39] and among older adults[10], but is avoided in the stroke population due to its perceived adverse enhancing effects on spasticity.[4] However, a recent study indicates that spasticity exhibits no such increase during hemiplegic gait.[5] When the hemiplegic leg is weighted an immediate effect is noticed on walking speed. This speed is reduced, but appears to catch up with further practice and increased motor activity (Table 2). As a result foot clearance appears to improve gradually within the B phases and subsequent initial A phases. With the mass applied distally to the hemiparetic extremity the effects on walking speed may be the result of the weight (mass) and/or inertia caused by the swaying limb. A more or less pendulous motion is elicited. In order to differentiate between these two modes of action weights applied to the center of mass of the extremity involved may be necessary. Ultimately this therapeutic intervention would generate feasible implications only if carry-over or hysteresis** effects could be established between the A_1 phase and other A phases. Short term rather than long term effects were studied because if present carry-over effects are presumed to occur immediately following cessation of the therapeutic weighting. Possible long term effects may require long term practice.

This pilot study suffered from imperfections and limitations with regard to applied weights, parameters and research design. Therefore, it may have been unsuited to detect minor therapeutic carry-over effects if present. In healthy subjects, paretic gait can be simulated by applying increasing weights (2–6 kg) around the ankles.[40] Based on empirical grounds, arbitrary weights of 2 lbs and 6 lbs were selected for this study. Clinically, possible limits to the maximal tolerated or ideal amount of overloading are dependent upon body weight and the degree of paresis. Therefore, overloading based on a percentage of body mass and degree of paresis is recommended when conducting such a study. Only the effects of overloading on walking speed were studied. However, other temporal parameters such as phase differences between arm and leg swing[41], angular joint displacements, stride duration, symmetry ratios, truncal rotation, individual phase durations and proportions, foot clearance as well as stability or muscle strength may be affected, but these parameters were not measured. A future research endeavour will investigate the effects of overloading on these gait parameters. Finally, a single subject research design lacks external validity and as a consequence it is difficult to generalize the results of individual patients to other stroke victims.

** Hysteresis is a retardation of the effect when the forces acting upon a body are changed.

CONCLUSION

This single subject design study found no limb overloading induced carry-over group effects on ensuing control phases. At a subject level only one patient showed a significant carry-over effect between the A_1 and A_2 phases. Moreover, although gradual improvements in comfortable walking speed between subsequent days were found this pilot study did not demonstrate favourable group effects on comfortable walking speed as a result of limb overloading. However, due to the limited carry-over effect found in one subject and because all patients perceived overloading as to facilitate gait and reduce heaviness of the paretic extremity, further kinematic research within a larger trial will be conducted to elucidate possible benefits to this approach in improving hemiplegic gait in stroke patients.

REFERENCES

1. Bohannon RW, Andrews AW, Smith M.B. Rehabilitation goals of patients with hemiplegia. International Journal of Rehabilitation Research. 1988; 11: 181–183.
2. Nilsson LM, Nordholm LM. Physical therapy in stroke rehabilitation: Bases for Swedish physiotherapists' choice of treatment. Physiotherapy Theory and Practice. 1992; 8: 49–55.
3. Sackley CM, Lincoln NB. Physiotherapy treatment for stroke patients: A survey of current practice. Physiotherapy Theory and Practice. 1996; 12: 87–96.
4. Bobath B. Adult Hemiplegia: Evaluation and Treatment (2nd ed.). William Heinemann Medical Books Limited, London. 1978.
5. Ada L, Vattanasilp W, O'Dwyer NJ, Crosbie J. Does spasticity contribute to walking dysfunction after stroke? Journal of Neurology, Neurosurgery and Psychiatry. 1998; 64: 628–635.
6. Bourbonnais D, Vanden Noven S. Weakness in patients with hemiparesis. American Journal of Occupational Therapy. 1989; 43: 313–319.
7. Fellows SJ, Ross CKHF, Thilmann AF. Agonist and antagonist EMG activation during isometric torque development at elbow in spastic hemiparesis. Electromyography and Clinical Neurophysiology. 1994; 93: 106–112.

8. Gowland C, De Bruin H, Basmajian JV, Plews N, Burcea I. Agonist and antagonist activity during voluntary upper-limb movement in patients with stroke. Physical Therapy. 1992; 72: 624–633.
9. O'Dwayer NJ, Ada L, Neilson PD. Spasticity and muscle contracture following stroke. Brain. 1996; 119: 1737–1749.
10. Brill PA, Probst JC, Greenhouse DL, Schell B, Macera CA. Clinical feasibility of a free-weight strength-training program for older adults. Journal of the American Board of Family Practice. 1998; 11: 445–451.
11. Brown DA, Kautz SA. Increased workload enhances force output during pedalling exercise in persons with poststroke hemiplegia. Stroke. 1998; 29: 598–606.
12. Miller GJT, Light KE. Strength training in spastic hemiparesis: Should it be avoided? NeuroRehabilitation. 1997; 9: 17–28.
13. Sharp SA, Brouwer BJ. Isokinetic Strength training of the hemiparetic knee: Effects on function and spasticity. Archives of Physical Medicine and Rehabilitation. 1997; 78: 1231–1236.
14. Bourbonnais D, Bilodeau S, Cross I, Lemay JF, Caron S, Goyette M. A motor re-education programme aimed to improve strength and co-ordination of the upper limb of a hemiparetic subject. NeuroRehabilitation. 1997; 9: 3–15.
15. Butefisch C, Hummelsheim H, Denzler P, Maurtiz KH. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. Journal of the Neurological Sciences. 1995: 130: 59–68.
16. Engardt M, Knutsson E, Jonsson M, Sternhag M. Dynamic muscle strength training in stroke patients: Effects on knee extension torque, electromyographic activity, and motor function. Archives of Physical Medicine and Rehabilitation. 1995; 76: 419–425.
17. Giuliani C. Strength training for patients with neurological disorders. Neurology Report. 1995; 19: 29–34.
18. Mercier C, Bourbonnais D, Bilodeau S, Lemay JF, Cross P. Description of a new motor re-education programme for the paretic lower limb aimed at improving the mobility of stroke patients. Clinical Rehabilitation. 1999; 13: 199–206.
19. Teixeira-Salmela LF, Olney SJ, Nadeau S, Brouwer B. Muscle strengthening and physical conditioning to reduce impairment and disability in chronic stroke survivors. Archives of Physical Medicine and Rehabilitation. 1999; 80: 1211–1218.

20. Aniss AM, Gandevia SC, Milne RJ. Changes in perceived heaviness and motor commands produced by cutaneous reflexes in man. Journal of Physiology. 1988; 397: 113–126.
21. Gandevia SC, Macefield VG, Bigland-Ritchie B, Gorman RB, Burke D. Motoneuronal output and graduation of effort in attempts to contract acutely paralysed leg muscles in man. Journal of Physiology. 1993; 471: 411–427.
22. Milne RJ, Aniss AM, Kay NE, Gandevia SC. Reduction in perceived intensity of cutaneous stimuli during movement: A quantitative study. Experimental Brain Research. 1988; 70: 569–576.
23. Kazdin AE. Single-Case Research Designs: Methods for Clinical and Applied Settings. Oxford University Press, New York. 1982.
24. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scandinavian Journal of Rehabilitation. 1975; 7: 13–31.
25. Badke MB, Duncan PW. Patterns of rapid motor responses during postural adjustments when standing in healthy subjects and hemiplegic Patients. Physical Therapy. 1983; 63: 13–20.
26. Brandstater MA, De Bruin H, Gowland C, Clark BM. Hemiplegic gait: Analysis of temporal variables. Archives of Physical Medicine and Rehabilitation. 1983; 64: 583–587.
27. Dettmann MA, Linder MT, Sepic SB. Relationships among walking performance, postural stability, and functional assessments of the hemiplegic patient. American Journal of Physical Medicine. 1987; 66: 77–90.
28. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke – outcome assessment and sample size requirements. Stroke. 1992; 23: 1084–1089.
29. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. Physical Therapy. 1993; 73: 447–454.
30. Roth EJ, Merbitz C, Mroczek K, Dugan SA, Suh WW. Hemiplegic gait – relationship between walking speed and other temporal parameters. American Journal of Physical Medicine and Rehabilitation. 1997; 76: 128–133.
31. Bohannon RW. Strength of lower limb related to gait velocity and cadence in stroke patients. Physiotherapy Canada. 1986; 38: 204–206.

32. Bohannon RW. Gait Performance of hemiparetic stroke patients: Selected variables. Archives of Physical Medicine and Rehabilitation. 1987; 68: 777–781.
33. Bohannon RW. Selected determinants of ambulatory capacity in patients with hemiplegia. Clinical Rehabilitation. 1989; 3: 47–53.
34. Turnbull GI, Wall JC. The development of a system for the clinical assessment of gait following a stroke. Physiotherapy. 1985; 71: 294–300.
35. Wall JC, Ashburn A. Assessment of gait disability in hemiplegics. Scandinavian Journal of Rehabilitation. 1979; 11: 95–103.
36. Wall JC, Turnbull GI. Gait asymmetries in residual hemiplegia. Archives of Physical Medicine and Rehabilitation. 1986; 67: 550–553.
37. Collen FM. The measurement of standing balance after stroke. Physiotherapy Theory and Practice. 1995; 11: 109–118.
38. Wade D. Measurement in Neurological Rehabilitation. Oxford University Press, Oxford 1992.
39. Mazur LJ, Yetman RJ, Risser WL. Weight-training injuries. Sports Medicine. 1993; 16: 57–63.
40. Eke-Okoro ST, Larsson L-E, Sandlund B. Simulation of paretic gait in normal subjects by loading the ankles. Scandinavian Journal of Rehabilitation. 1985; 17: 147–150.
41. Wagenaar RC, Beek WJ. Hemiplegic gait: A kinematic analysis using walking speed as a basis. Biomechanics. 1992; 25: 1007–1015.

CHAPTER 8

Long term effects of intensity of upper and lower limb training after stroke: A randomised trial

Gert Kwakkel, Boudewijn Kollen, and Robert Wagenaar

Journal of Neurology, Neurosurgery and Psychiatry 2002; 72: 473–479

Abstract

Objective:

To assess long term effects at 1 year after stroke in patients who participated in an upper and lower limb intensity training programme in the acute and subacute rehabilitation phases.

Design:

A three group randomised controlled trial with repeated measures was used.

Method:

One hundred and one patients with a primary middle cerebral artery stroke were randomly allocated to one of three groups for a 20 week rehabilitation programme with an emphasis on (1) upper limb function, (2) lower limb function or (3) immobilisation with an inflatable pressure splint (control group). Follow up assessments within and between groups were compared at 6, 9, and 12 months after stroke.

Results:

No statistically significant effects were found for treatment assignment from 6 months onwards. At a group level, the significant differences in efficacy demonstrated at 20 weeks after stroke in favour of the lower limb remained. However, no significant differences in functional recovery between groups were found for Barthel index (BI), functional ambulation categories (FAC), action research arm test (ARAT), comfortable and maximal walking speed, Nottingham health profile part 1 (NHP-part 1), sickness impact profile-68 (SIP-68), and Frenchay activities index (FAI) from 6 months onwards. At an individual subject level a substantial number of patients showed improvement or deterioration in upper limb function (n = 8 and 5, respectively) and lower limb function (n = 19 and 9, respectively). Activities of daily living (ADL) scores showed that five patients deteriorated and four improved beyond the error threshold from 6 months onwards. In particular, patients with some but incomplete functional recovery at 6 months are likely to continue to improve or regress from 6 months onwards.

CONCLUSIONS:

On average patients maintained their functional gains for up to 1 year after stroke after receiving a 20 week upper or lower limb function training programme. However, a significant number of patients with incomplete recovery showed improvements or deterioration in dexterity, walking ability, and ADL beyond the error threshold.

INTRODUCTION

Recently, small but significant overall effect sizes were found in favour of higher intensity of a stroke rehabilitation programme after pooling the findings of nine controlled trials.[1] In a recent randomised controlled trial, Kwakkel et al provided more evidence for larger effect sizes as a result of higher intensity of upper and lower limb training in terms of activities of daily living (ADL), walking ability, and dexterity.[2] They attributed these favourable effects to factors within the design — that is, (1) increased treatment contrast between control and experimental treatment, (2) reduced heterogeneity of included patients with regard to neurological diagnosis and disability, and (3) optimal use of scaling properties of assessment instruments.[2] In addition, effects of rehabilitation seemed to be more pronounced within the first months after stroke, whereas little recovery took place thereafter. However, the question whether reported differences in treatment efficacies could still be discerned at 1 year after stroke was not addressed in this study. The findings of several studies suggest that most patients maintain their achieved gains of rehabilitation in terms of ADL,[3–7] walking ability,[5] and dexterity[7] 6 months after stroke. Others indicated small but significant continuation of functional recovery up to 2 years after stroke,[8] particularly in response to a task oriented treatment programme.[9–16] However, some studies reported deterioration in disability, especially when patients were discharged home without adequate rehabilitative support.[17,18] In addition, it was found that severity of neurological impairments and disabilities in the first 6 months were indicative of the long term prognosis at 1 or 2 years after stroke.[7,11] The objectives of the present study were (1) to determine if treatment effects are maintained within and between treatment groups from 6 months to 1 year after stroke, and (2) to identify those patients who are likely to show significant improvement or deterioration in ADL, walking ability, and dexterity from 6 months onwards.

SUBJECTS AND METHODS

Patients

The patients with stroke participating in the present study (1) had had a primary, first ever stroke in the territory of the middle cerebral artery (MCA) as shown by CT or MRI, (2) were between 30 to 80 years of age, (3) had an impaired motor function of upper as well as lower limbs, (4) were unable to walk at first assessment, (5) had no complicating medical history such as cardiac, pulmonary, or other neurological disorders, (6) had no severe deficits in communication, memory, or understanding, and (7) gave written or verbal informed consent, and were sufficiently motivated to participate in the research project. Stroke was defined clinically according to the World Health Organisation criteria[19] and classified according to the Bamford classification using clinical features to determine the size and site of infarct.[20] These subtypes are total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), and lacunar infarcts (LACI).[20]

Within 24 hours after stroke onset, patients were assessed by a neurologist to confirm the clinical diagnosis of stroke and to record clinical symptoms such as level of consciousness [assessed with the Glasgow coma scale (GCS)].[21] A speech therapist assessed the ability to communicate, and accepted a cut off of 50 percentile corrected for age on the Dutch Foundation aphasia test (SAN).[22] The mini mental state examination (MMSE) was applied to screen the orientation in time and place. Only patients with an MMSE score of 24 points or higher were included in the trial.[23] In addition, sitting balance were assessed with the trunk control test.[24] Homonymous hemianopia was identified by confrontation and visual inattention was assessed by the letter cancellation task.[25] Conjugate gaze deficit was diagnosed when there was a failure of conjugate gaze towards the paretic body side. Finally, social support was defined as having a healthy partner willing and able to support the patient in care.

To control for the heterogeneity of the stroke population, muscle strength, balance, proprioception, and cognitive function were assessed following the Orpinton prognostic scale (OPS).[26]

Design

Within 14 days of stroke, 101 patients with a primary, first ever stroke in the territory of the middle cerebral artery were randomly assigned to one of the three treatment groups.[2] The control group was designed for patients subjected to immobilisation of the paretic arm and leg by means of an inflatable pressure splint.[27] The splint (Svend Andersen, plastic industrials, Haarlev, Denmark®) was applied to the supine patient for 30 minutes each day, 5 days a week for 20 weeks.[27,28] The two experimental groups received 30 minutes lower limb or upper limb training, 5 days a week for 20 weeks. In addition, all three groups received 15 minutes of lower limb rehabilitation, 15 minutes of upper limb rehabilitation, and 1.5 hours of weekly ADL training. The ADL training was carried out by an occupational therapist. After finishing the treatment protocol, from 20 weeks onwards, decisions about type of treatment and its intensity were made by the stroke management team taking care of the individual patient. Ethical approval was given by each participating hospital.[2]

Treatment conditions

The treatment programme was based on a protocol comprising evidence based guidelines. A task oriented therapeutic approach was advocated. Upper limb treatment was focused on improvement in disabilities involving the hemiplegic arm (for example, grasping, reaching, leaning, clothing), whereas lower limb treatment was focused on the functional recovery of balance (for example, sitting, standing balance), transfers such as turning over, and gait (for example, performance and climbing stairs). The treatment goals were registered daily by predefined codes in a diary. The frequency of applied treatment goals is summarised in Table 1. Differences in treatment duration are presented elsewhere.[2]

Table 1. Documented frequencies of selected goals for treatment.

Training of activities	Frequency of applied treatment goals during first 20 weeks			
	CT	UL	LL	*p* Value*
Air splint application	2504	0	0	0.000
Lower limb training:				
Impairments (for example, muscle strength and ROM)	517	434	655	0.475
Transfers	361	310	484	0.291
Sitting balance, sitting up from lying position	576	531	604	0.690
Standing balance	716	656	669	0.449
From sitting to standing/standing up from lying position	592	692	676	0.436
Gait: coordination, stability, symmetry, and velocity	1130	1225	1649	0.324
Climbing stairs, walking over uneven surfaces and doorsteps	366	332	703	0.069
Outdoor walking	215	168	367	0.185
Learning to use a walking aid	219	123	367	0.235
Other lower limb functions	278	129	351	0.164
Upper limb training:				
Impairments (for example, muscle strength and range of motion)	1778	1280	1991	0.164
Postural reactions and weight bearing	821	1346	871	0.580
Reaching, grasping activities	489	1054	724	0.189
Personal hygiene (for example, dressing, cooking, washing, and combing)	431	829	585	0.441
Application of sling or orthosis	11	26	19	0.808
Other functions	379	583	257	0.279

* χ^2 test; CT, control group; UL, upper limb; LL, lower limb

Assessments

Primary outcome variables included the Barthel index (BI), functional ambulation categories (FAC) and the action research arm test (ARAT). The Dutch version of the BI is a reliable and valid measurement that represents a patient's ability to perform 10 ADL tasks (bladder and bowel control, toilet use, dressing, feeding, ambulation, personal toilet, transfer activities, bathing, and stair climbing).[29] The FAC measures six levels of walking ability and documents personal support needed during walking with or without aid, and has been described as a reliable and valid measurement.[30] Functional recovery of the upper limbs was monitored with the ARAT.[31] This test consists of 19 functional movement tasks which are divided into four domains (grasp, grip, pinch, and gross movement). The BI, FAC, and ARAT were reassessed for their within observer reliability in 15 patients with stroke using a 1 week interval between measurements. Spearman rank correlation coefficients (r_s) were 0.97 for BI and FAC, and 0.99 for the ARAT test ($p < 0.001$). Secondary variables of outcome included comfortable and maximal walking speeds by means of a 10 m timed walking test.[32] The tests showed high test-retest reliability ($r_s = 0.97$, $p < 0.001$ and $r_s = 0.96$, $p < 0.001$, respectively). In addition, the number of applied walking devices was monitored. Part 1 of the Nottingham health profile (NHP-part 1)[33] and a short generic version of the sickness impact profile (SIP-68)[34,35] were used to assess quality of life. The first part of the NHP consists of 38 items (yes/no questions) describing health related behaviour in six dimensions (or domains of daily life; energy, physical mobility, sleep, pain, emotional reactions, and social isolation).[33] High scores indicate a poor health status.

Test-retest reliability of the Dutch version of the NHP-part 1 has been demonstrated by Erdman et al.[33] The SIP-68 evaluates six domains of health related functional status (somatic autonomy, mobility control, psychological autonomy, communication, social behaviour, emotional stability, and mobility range), explaining 94% of the total variance of the original SIP-136.[34] A high score indicates poor health related functional status. Post et al have demonstrated its high validity and reliability.[34] Extended ADLs were assessed with the Frenchay activities index (FAI).[35] The first part of the FAI evaluates the frequency of performance of 10 activities (preparing meals, washing up, washing clothes, light and heavy housework, social outings, local shopping, walking outside (> 15 minutes), actively pursuing a hobby, and driving a car or travelling by bus) during the last 12 weeks, whereas five activities (outings and car rides, gardening, household maintenance, reading books, and gainful working) performed in the last 26 weeks are evaluated in the second part. Schuling et al[36] have demonstrated its reliability and validity. All primary and secondary outcome variables were assessed at 6, 9, and 12 months after stroke. Within the first 6 months all measurements were carried out by one investigator (GK) who was blinded for treatment assignment.

However, 6 months after stroke the blinding procedure was released. Depending on stroke severity, the test battery took about 45 to 75 minutes to complete.

Statistics

Group level

The Kruskal-Wallis test was applied to evaluate the differences between the three groups at 9 and 12 months after stroke for BI, FAC, ARAT, comfortable and maximal walking velocity, number of walking devices, SIP-68, and NHP-part (SPSS version 9.0.) The same tests were applied to evaluate possible differences between groups for changes on FAI from baseline to 6 months and from 6 to 12 months after stroke. When significant differences between three groups were found a post hoc analysis was performed using the Mann-Whitney *U* test to demonstrate which group differed significantly from the other.
To establish any significant improvement or deterioration from 6 months onwards in the complete group as well as within each group, changes in BI, FAC, ARAT, SIP-68, and NHP part 1 scores were tested with a Friedman two way analysis of variance (ANOVA) by ranks. If significant findings were obtained, a post hoc Wilcoxon matched pairs signed ranks test for non-continuous outcome variables was applied to evaluate the differences in outcomes at 6, 9, and 12 months. Outcome in FAI was tested at 6 and 12 months by applying a Wilcoxon matched pairs signed ranks test. After testing interval scaled measurements for normality with the Kolomogorov-Smirnov test, a paired sample *t* test was used to demonstrate differences in comfortable and maximal walking speeds.

Subject level

To show whether patients showed significant recovery or deterioration in functional status from 6 months onwards, measurement errors (error thresholds) were calculated and compared to the actual changes in BI, FAC, ARAT, comfortable and maximal walking speed. The error threshold was calculated on the basis of two independent measurements taken at 9 and 10 weeks after stroke. Based on the assumption that the errors of the two measurements are independent from each other, the within subject variance was determined. Subsequently, the standard error of measurement (SEM) was calculated from the square root of the within subject variance assuming that the difference between two independent measurements should be at least 1.96√2xSEM to meet the criterion of a 95% confidence level of a real difference between the true scores.[37,38]

Finally, the error threshold for each variable of outcome was rounded off and the number of patients who improved or deteriorated beyond the error threshold after 6 months was determined.

RESULTS

Eighty six (85%) out of 101 patients were reassessed at 9 and 12 months after stroke onset. During the first year follow up period four patients dropped out from the control group, five in the upper limb, and six in the lower limb group. Twelve out of these patients dropped out before week 20 (three control group, four upper limb group, and five lower limb group).[2] Recurrent stroke (n = 6), comorbidity (for example, cancer) (n = 2), and death from cardiac failure (n = 2) were the most common reasons.

In total 1750 (96.3%) of the intended 1818 measurements were performed. The amount of upper limb training administered during the 20 week treatment protocol in the upper limb group (3860 minutes) was about 2250 minutes and 2080 minutes in excess of upper limb function training provided to the controls and lower limb group, respectively.

The lower limb group received about 3660 minutes of lower limb training, which was about 2270 and 2320 minutes more than the lower limb function training provided to the control group and upper limb group, respectively. After 6 months, 68% of the patients (n = 59) were discharged home, whereas 52.5% (n = 53) were still ADL dependent (BI < 19). They received one to three weekly treatment sessions of 30 minutes, depending on their personal needs. Almost all rehabilitation services were performed at the institution of discharge. For patients who were considered to be ADL independent, rehabilitation was stopped. At 1 year after stroke, patients included in the trial were not receiving any type of physical or occupational therapy.

Table 2. Baseline characteristics of patients.

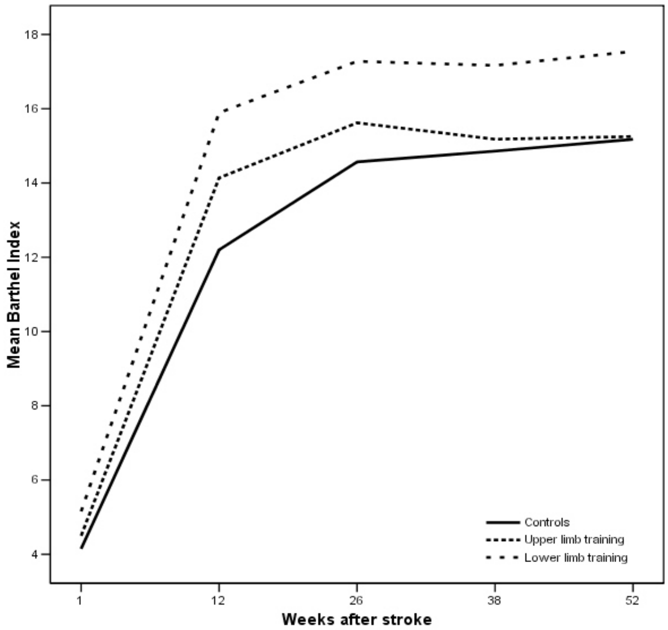
	Control treatment (n=37)	**UL training** (n=33)	**LL training** (n=31)
Demography:			
M/F	14/23	16/17	13/18
Age (y)*	64.1 (15.0)	69.0 (9.8)	64.5 (9.7)
Stroke characteristics:			
Left/right	13/24	16/17	13/18
TACI	25	19	17
PACI	9	11	13
LACI	3	3	1
Clinical characteristics:			
Glasgow coma scale (0–15)†	15 (15–15)	15 (15–15)	15 (15–15)
MMSE (0–30)†	26 (24–28)	27 (24–29)	27 (26–29)
Urinary incontinence (0/1)	19 (51%)	19 (58%)	11 (35%)
Sitting balance (0/1)	26 (70%)	23 (70%)	25 (81%)
Visual gaze deficit (0/1)	12 (32%)	8 (24%)	5 (16%)
Hemianopia (0/1)	15 (41%)	11 (33%)	7 (23%)
Visual inattention (0/1)	20 (54%)	17 (51%)	14 (45%)
TFT score (0–3)†	1 (0.5–2)	1 (0–2)	1 (0–2)
OPS (1.6–6.8)†	4.8 (4.0–5.0)	4.4 (3.6–5.2)	4.2 (3.6–4.8)
Social support	14 (38%)	15 (45%)	11 (35%)
Outcome variables at baseline:			
ADL ability (BI)†	5.5 (3–7)	5 (3–7)	6 (3–8)
Walking ability (FAC)†	0 (0–1)	0 (0–1)	1 (0–2)
Dexterity (ARAT)†	0 (0–0)	0 (0–1)	0 (0–6)
Walking velocity (m/s)*	0 (0)	0 (0)	0 (0)
Frenchay activities index*	26.8 (6.8)	26.5 (6.1)	27.1 (7.0)
Nottingham health profile*	16.5 (6.7)	17.5 (9.3)	14.5 (6.4)
Sickness impact profile*	41.2 (11.7)	38.6 (10.9)	42.5 (6.5)
Time from stroke onset to start of treatment (days)*	7.5 (2.9)	7.2 (2.8)	7.0 (2.5)

* Mean (SD); † median (IQR). (0/1), binary scored; UL, upper limb; LL, lower limb; M/F, male/female; TACI, total anterior cerebral infarct; PACI, partial anterior cerebral infarct; LACI, lacunar infarct; MMSE, mini mental state examination; TFT, thumb finding test; OPS, Orpington prognostic scale

Group level

The results of the primary and secondary outcomes at baseline, 6, 9, and 12 months are shown in Tables 2, 3, and 4, respectively. The mean pattern of functional recovery in BI for patients receiving control group, upper limb, and lower limb treatment is presented in Figure 1. Visual inspection of the mean functional recovery in BI suggests that the increased outcome as the result of higher intensity of rehabilitation carried over to 9 and 12 months after stroke.

Figure 1. Recovery patterns for patients as measured by the Barthel index.



However, no significant differences in functional recovery between groups were found for BI, FAC, ARAT, comfortable and maximal walking speed, NHP-part 1, SIP-68, and FAI from 6 months onwards. Within the included (total) patient group no significant changes between outcomes at 6 months and 12 months were found within the included (total) patient group in BI ($\chi^2_{n=2} = 2.50$; $p = 0.29$), FAC ($\chi^2_{n=2} = 3.88$; $p = 0.14$), ARAT ($\chi^2_{n=2} = 4.01$; $p = 0.13$), comfortable ($\chi^2_{n=2} = 3.31$; $p = 0.19$) and maximal walking speed ($\chi^2_{n=2} = 4.92$; $p = 0.09$), NHP-part 1 ($\chi^2_{n=2} = 2.41$; $p = 0.30$), and SIP-68 ($\chi^2_{n=2} = 3.12$; $p = 0.21$). Only the FAI score at 12 months was significantly higher (about 2 points) compared with the score obtained at 6 months after stroke ($Z = 5.17$; $p < 0.001$). Comparing the outcomes at 6 months and 12 months after stroke, no significant changes were found within the three patient groups for primary and secondary variables of outcome. Only maximal walking speed in the control group showed a significant improvement from 6 months onwards ($t = 2.29$; $p = 0.03$).

Table 3. Primary outcomes.

	Median (IQR) value		
	Control group (n=37)	**UL training group** (n=33)	**LL training group** (n=31)
ADL ability (Barthel index):			
Week 26	17 (10.5–19)	17 (11.75.20)	19 (15–20)
Week 38	17 (12.5–18.25)	17 (10.5–20)	17.5 (15.25–20)
Week 52	17 (14–20)	15 (12.5.20)	18 (14.5–20)
Change beyond ET after 6 months (n=86):			
Number improved ≥ 4 points	3	1	0
Number deteriorated ≥ 4 points	1	2	2
Walking ability (functional ambulation categories):			
Week 26	4 (2–5)	4 (3–5)	5 (4–5)
Week 38	4 (3–5)	4 (3–5)	5 (4–5)
Week 52	4 (3–5)	4 (3–5)	5 (4–5)
Change beyond error threshold after 6 months (n=86):			
Number improved ≥ 1 point	11	4	4
Number deteriorated ≥ 1 point	2	6	1
Dexterity (action research arm test):			
Week 26†	0 (0–2.25)	4 (0–38)**	3 (0–56)*
Week 38	0.5 (0–20.5)	5 (0–38.5)	5 (0–51.5)
Week 52	1 (0–28.5)	6 (0–42.25)	6 (0–52.75)
Change beyond error threshold after 6 months (n=86):			
Number improved ≥ 5 points	2	4	2
Number deteriorated ≥ 5 points	0	3	2

*$p < 0.05$; **$p < 0.01$ for differences between experimental and control group;
† $p < 0.01$ for significant difference among groups (Kruskal-Wallis ANOVA test).
UL, upper limb; LL, lower limb

Subject level

The responsiveness of the primary outcome assessments (BI, FAC, ARAT) and secondary outcome assessments (comfortable and maximal walking speed) are shown in Tables 3 and 4.

Table 4. Secondary outcomes.

	Mean (SD) value		
	Control group (n=37)	**UL training group** (n=33)	**LL training group** (n=31)
Comfortable walking speed (m/s):			
Week 26	0.44 (0.44)	0.55 (0.44)	0.63 (0.47)
Week 38	0.52 (0.46)	0.59 (0.44)	0.65 (0.45)
Week 52	0.53 (0.44)	0.59 (0.43)	0.64 (0.46)
Change at individual level > 6 months:			
Number improved ≥ 0.16 m/s	6	2	2
Number deteriorated ≥ 0.16 m/s	2	2	6
Maximal walking speed (m/s):			
Week 26	0.57 (0.60)	0.73 (0.62)	0.85 (0.65)
Week 38	0.67 (0.61)	0.76 (0.58)	0.86 (0.62)
Week 52	0.71 (0.62)	0.88 (0.67)	0.85 (0.63)
Change at individual level after 6 months:			
Number improved ≥ 0.18 m/s	8	6	4
Number deteriorated ≥ 0.18 m/s	2	3	7
Used walking aids:			
Week 26	17 (49%)	17 (57%)	14 (53%)
Week 38	21 (60%)	17 (61%)	16 (69%)
Week 52	20 (59%)	19 (68%)	15 (63%)
Sickness impact profile:*			
Week 26	32.9 (12.0)	27.9 (13.1)	25.7 (12.7)
Week 38	32.0 (12.2)	28.5 (13.7)	24.2 (14.3)
Week 52	31.2 (11.6)	26.9 (13.1)	26.1 (14.1)
Nottingham health profile:*			
Week 26	11.5 (7.9)	9.5 (5.9)	9.8 (8.1)
Week 38	11.8 (7.4)	10.6 (7.4)	10.4 (8.5)
Week 52	11.7 (8.4)	9.0 (6.0)	11.6 (9.6)
Frenchay activities index:			
Week 26	8.2 (7.8)	10.9 (8.3)	13.7 (9.5)
Week 52	12.0 (8.3)	12.7 (9.1)	15.7 (11.7)

*High scores indicate poor status. UL, upper limb; LL, lower limb

The calculated error thresholds for BI, FAC, and ARAT were 4, 1, and 5 points, respectively. In Tables 3 and 4 the number of patients improving or deteriorating significantly from 6 months to 1 year is presented. Four out of 86 patients continued to improve in BI score (median five points; range 5–7), 19 in FAC score (mean 1 point; range 1–3), and eight in ARAT score (median 8.5, range 6–24). Most of the patients improving in FAC score were participating in the control group (n = 11), however, the differences between groups were not statistically significant. At 6 months, median scores for patients who improved in BI, FAC, and ARAT were 9.5 (IQR: 9–10.75), 2 (IRQ: 1–4), and 21 (IQR: 1.5–45.75) points, respectively.

Five patients showed significant deterioration from 6 months to 1 year in BI (mean five points; range 4–6), nine patients in FAC score (median 1; range 1–3) and five patients in ARAT score (mean 11; range 6–13). No significant differences were found between the three treatment groups. However, the median scores and interquartile ranges (IQR) for patients who deteriorated corresponded to incomplete functional recovery on BI (16; IQR 9–17), FAC (4; IQR 2–4) and ARAT (41; IQR 19.5–54), 6 months after stroke.

The error thresholds for comfortable (0.16 m/s) and maximal (0.18 m/s) walking speeds are presented in Table 4. From 6 months to 1 year, 10 patients (six controls, two upper limb, and two lower limb) improved significantly from 0.38 to 0.64 m/s in comfortable walking speed, whereas during the same period 18 patients (eight controls, six upper limb, and four lower limb) improved from 0.60 to 0.73 m/s in maximal walking speed (Table 4). Ten patients deteriorated in comfortable walking speed (two controls, two upper limb, and six lower limb) and 12 patients in maximal walking speed (two controls, three upper limb, and seven lower limb).

DISCUSSION

The first objective of this follow up study was to determine the long term effects of an intensive rehabilitation programme for upper and lower limb function training during the first year after stroke.

With the exception of a significant recovery of maximal walking speed in the control group, no significant between and within group differences were found for ADL, extended ADL, walking ability, dexterity, comfortable walking speed, and health related functional status between 6 and 12 months after stroke.
The significant recovery in maximal walking speed in the control group may have been due to a slow and late recovery as a result of immobilisation of an upper and lower limb during the first 20 weeks after stroke onset. The ability of the stroke management teams to make their own decisions about individual patient care after ending the 20 week intense treatment programme may have contributed to improvements, in particular for those who were immobilised.
The present findings confirm the results of other studies indicating that higher intensity of upper and lower limb function training during the first 6 months after stroke did not result in significant gains at 1 year, even though this training accelerated speed of functional recovery[4,6,7] and improved health related functional status during the first 3 months after stroke.[2] However, the absence of functional recovery at group level does not imply that no changes occurred at an individual subject level. Therefore, the second objective of the present study was to identify those patients who showed functional changes beyond the error threshold after 6 months. Although the present findings suggest that most functional levels achieved after stroke were maintained after 6 months, individually some patients tended to improve or regress in their functional ability beyond the critical 95% level of measurement error. All patients who changed significantly from 6 months onwards showed some but incomplete functional recovery at 6 months after stroke. For example, patients who improved or regressed at least 4 points or more in BI score after 6 months (n = 9) showed a median score of 11 points on the BI at 6 months, whereas 28 patients (33%) who showed further improvement or deterioration on the FAC score were only able to walk under supervision (median of 3 points on FAC). Moreover, some of these patients showed significant changes in comfortable (23%) and maximal (34%) walking speeds. In agreement with the deteriorations in FAC scores, most patients showed low comfortable [0.38 (SD 0.41) m/s] and maximal [0.53 (SD 0.44) m/s] walking speeds at 6 months. Finally, 13 patients (15%) showed

further changes of at least five points in the ARAT score. Again, patients with incomplete functional recovery of the upper limb on the ARAT test (median of 37 points) are likely to change beyond the error threshold.

The presented findings for BI and FAC indicated that most of these patients were not able to get dressed, take a bath, transfer, walk and climb stairs independently. Most likely, the present findings reflect the long term instability of achieved gains, in particular for those patients who have regained some, but still incomplete functional activity at 6 months after stroke. Several randomised controlled studies have shown that those with an incomplete functional recovery are able to improve walking ability,[10,16] dexterity,[12,14–16] and ADL[13,39,40] when those tasks are included in their therapeutic programme. In addition, proper instruction to patient and caregiver to prevent overprotection at home,[17,18,41] participation in recreational sports, and application of strategies to improve the self care and self efficacy[42] may be important elements in a rehabilitation programme for establishing further recovery and preventing learned non-use after discharge. It may be hypothesised that the implementation of the intensive, task oriented exercise programme beyond the first 20 weeks results in further improvements in functional recovery, in particular for those with an incomplete recovery. However, more than half of the patients did not receive physical or occupational therapy more than 6 months after stroke. With the exception of one patient, intensity of therapy was less compared with the treatment intensity during the first 20 weeks after stroke in the group of patients that did continue therapy after 6 months. At 1 year, none of the patients with stroke received any rehabilitation services. Most likely this finding reflects the general assumption among healthcare providers that individual changes more than 6 months after stroke will be limited and not clinically relevant. Due to a lack of systematic manipulation and control for intensity and content of rehabilitation services provided after 6 months, we were unable to demonstrate the long term effects of intensity of treatment on the individual patterns of functional recovery between 6 and 12 months after stroke. In addition, we cannot rule out possible observation bias due to elimination of blinding of the observer 6 months after stroke. Future studies may be directed towards finding predictive factors of functional recovery more than 6 months after stroke. In addition, the effects of dose-response relations of task oriented treatment programmes in these patients with stroke showing an incomplete, but slow and persistent functional recovery should be investigated. Being able to identify these patients will allow for the administration of better individually tailored therapeutic interventions with regard to intensity, task specificity, and treatment frequency. Although, presently adequate identification of these patients is not possible, continuity in monitoring functional outcome will help therapists and physicians to decide the type and intensity of treatment needed to prevent further deterioration or to enhance improvement.[43]

Abbreviations:
SAN, Dutch Foundation aphasia test; MMSE, mini mental state examination; OPS, Orpinton prognostic scale; BI, Barthel index; FAC, functional ambulation categories; ARAT, action research arm test; NHP, Nottingham health profile; SIP, sickness impact profile; FAI, Frenchay activities index; ADL, activities of daily living.

REFERENCES

1. Kwakkel G, Wagenaar RC, Koelman TW, et al. Effects of intensity of stroke rehabilitation: A research synthesis. Stroke. 1997; 28: 1550–6.
2. Kwakkel G, Wagenaar RC, Twisk JWR, et al. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. Lancet. 1999; 354: 191–6.
3. Andrews K, Brocklehurst JC, Richards B, et al. The rate of recovery from stroke and its measurement. Internal Rehabilitation Medicine. 1981; 3: 155–61.
4. Sivenius J, Pyorala K, Heinonen OP, et al. The significance of intensity of rehabilitation of stroke: A controlled trial. Stroke. 1985; 16: 928–31.
5. Davidoff GN, Keren O, Ring H, et al. Acute stroke patients: Long-term effects of rehabilitation and maintenance of gains. Arch Phys Med Rehabil. 1991; 72: 869–73.
6. Indredavik B, Bakke F, Slørdahl SA, et al. Stroke Unit treatment 10 year follow-up. Stroke. 1999; 30: 1524–7.

7. Sunderland A, Fletcher D, Bradley L, et al. Enhanced physical therapy for arm function after stroke: A one year follow up study. J Neurol Neurosurg Psychiatry. 1994; 57: 856–8.
8. Katz S, Ford AB, Chinn AB, et al. Prognosis after stroke: Long term outcome of 159 patients. Medicine. 1966; 45: 236–46.
9. Tangeman PT, Banaitis DA, Williams AK. Rehabilitation of chronic stroke patients: changes in functional performance. Stroke. 1990; 71: 876–90.
10. Wade DT Collen FM, Robb GF, et al. Physiotherapy intervention late after stroke and mobility. BMJ. 1992; 304: 609–13.
11. Dam M, Tonin P, Casson S, et al. The effects of long-term rehabilitation therapy in poststroke hemiplegic patients. Stroke. 1993; 24: 1186–91.
12. Taub E, Miller NE, Novack TA, et al. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil. 1993; 74: 347–54.
13. Werner RA, Kessler S. Effectiveness of an intensive outpatient rehabilitation program for postacute stroke patients. Am J Phys Med Rehabil. 1996; 75: 114–20.
14. Dean CM, Shepherd RB. Task related training improves performance of seated reaching tasks after stroke: A randomized controlled trial. Stroke. 1997; 28: 722–8.
15. Lee van der JM, Wagenaar RC, Lankhorst GJ, et al. Forced use of the upper extremity in chronic stroke patients. Stroke. 1999; 30: 2369–75.
16. Dean CM, Richards CL, Malouin F. Task-related circuit training improves performance of locomotor tasks in chronic stroke: A randomized controlled trial. Arch Phys Med Rehabil. 2000; 81: 409–17.
17. Andrews K, Stewart J. Stroke recovery: He can but does he? Rheum Rehabil. 1979; 18: 43–8.
18. Ungern-Sternberg AV, Küthmann M, Weimann G. Stroke: Evaluation of long-term rehabilitation effects. J Neural Transm. 1991; 33(suppl): 149–55.
19. WHO Special report. Stroke: 1989: Recommendations on stroke prevention, diagnosis, and therapy. Stroke. 1989; 20: 1407–31.
20. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinical identifiable subtypes of cerebral infarction. Lancet. 1991; 337: 1521–6.
21. Teasdale G, Murray G, Parker L, et al. Adding up the Glasgow coma scale. Acta Neurochir. (Wien) 1979; 28: 13–6.

22. Deelman BG, Liebrand WBG, Koning-Haanstra, et al. SAN test: An aphasie test for language comprehension and linguistic usage. Construction and standards. Lisse: Swets and Zeitlinger BV. 1981.
23. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: A practical method for grading the cognitive state of patients for clinician. J Psychiatr Res. 1975; 12: 189–98.
24. Collin C, Wade DT. Assessing motor impairment after stroke: A pilot reliability study. J Neurol Neurosurg Psychiatry. 1990; 53: 576–80.
25. Beers KA. The cancellation test, report. Hoensbroeck: Rehabilitation Centre Hoensbroeck. 1986.
26. Kalra L, Crome P. The role of prognostic scores in targeting stroke rehabilitation in eldery patients. J Am Geriatr Soc. 1993; 41: 396–400.
27. Robichaud JA, Agostinucci J, Van der Linden DW. Effects of air-splint application on soleus muscle motorneuron reflex excitability in non-disabled subjects and subjects with cerebrovascular accidents. Phys Ther. 1992; 72: 176–81.
28. Poole JL, Whitney SL, Hangeland N, et al. The effectiveness of inflatable pressure splints on motor function in stroke patients. Occupational Therapy Journal of Research. 1990; 10: 360–5.
29. Haan de R, Limburg M, Schuling J, et al. Klinimetrische evaluatie van de Barthel-Index, een maat voor beperkingen in het dagelijks functioneren. Ned Tijdschr Geneesk. 1993; 137: 917–21.
30. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: Reliability of measures of impairment and disability. Int Disabil Studies. 1990; 12: 6–9.
31. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitated treatment and research. Int J Rehabil. 1981; 4: 483–92.
32. Hunt SM, McKenna SP, Williams J. Reliability of a population survey tool for measuring perceived health problems: A study of patients with osteoarthrosis. J Epidemiol Community Health. 1981; 35: 297–300.
33. Erdman RAM, Passchier J, Kooijman M, et al. The Dutch version of the Nottingham health profile: Investigations of psychometric aspects. Psychological Reports. 1993; 72: 1027–35.
34. Post MWM, DeBruin A, DeWitte L, et al. The SIP68: A measure of health related functional status in rehabilitation medicine. Arch Phys Med Rehabil. 1996; 77: 440–5.

35. Holbrook M, Skilbeck CE. An activities index for use with stroke patients. Age Ageing. 1983; 12: 166–70.
36. Schuling J, DeHaan M, Limburg, et al. The Frenchay activities index: Assessment of functional status in stroke patients. Stroke. 1993; 24: 1173–7.
37. Guyatt G, Walter S, Norman G. Measuring change over time: Assessing the usefulness of evaluation instruments. J Chron Dis. 1987; 40: 171–8.
38. Beckerman H, Vogelaar TW, Lankhorst GJ, et al. A criterion for stability of the motor function of the lower extremity in stroke patients using the Fugl-Meyer assessment scale. Scand J Rehabil Med. 1996; 28: 3–7.
39. Walker WF, Drummond AER, Lincoln NB. Evaluation of dressing practice for stroke patients after discharge from hospital: A crossover design study. Clin Rehabil. 1996; 10: 23–31.
40. Drummond AER, Walker MF. A randomised controlled trial of leisure rehabilitation after stroke. Clin Rehabil. 1995; 9: 283–90.
41. Morris DM, Crago JE, DeLuca SC, et al. Constraint-induced movement therapy for motor recovery after stroke. Neurorehabilitation. 1997; 9: 29–43.
42. Robinson-Smith G, Johnston MV, Allen J. Self-care self-efficacy, quality of life, and depression after stroke. Arch Phys Med Rehabil. 2000; 81: 460–4.
43. Kwakkel G, van Dijk GM, Wagenaar RC. Accuracy of physical and occupational therapists' early predictions of recovery after middle cerebral artery stroke. Clin Rehabil. 2000; 14: 28–41.

CHAPTER 9

Understanding the pattern of functional recovery after stroke: Facts and theories

Gert Kwakkel, Boudewijn Kollen, and Eline Lindeman

Restorative Neurology and Neuroscience 2004; 22: 281–299

Abstract

Longitudinal studies show that almost all stroke patients experience at least some predictable degree of functional recovery in the first six months post-stroke. However, the non-linear pattern as a function of time is not well understood.
Several mechanisms are presumed to be involved, such as recovery of penumbral tissues, neural plasticity, resolution of diaschisis and behavioural compensation strategies. Rehabilitation is believed to modulate this logistic pattern of recovery, probably by interacting with these underlying processes. However, prediction models that are adjusted for the effects of time after stroke onset suggest that outcome is largely defined within the first weeks post-stroke, although functional improvement has been found to extend beyond six months post-stroke. In addition, kinematic studies show that functional improvement is more than recovery from impairments alone, suggesting that patients are able to improve in terms of gait or dexterity deficits using behavioural compensation strategies. Therefore, understanding the impact of task-dependent cortical activation patterns in non-invasive methods requires not only information derived from longitudinal studies pertaining to functional outcomes, but also a better understanding of what is kinematically learned during the acquisition of new skills.

1.1 Understanding the effects of rehabilitation

In the absence of any curative therapy, rehabilitation is the most common treatment modality to improve quality of life after stroke.[37] Although primary prevention of stroke is crucial and remains paramount in the fight against stroke-induced disability, there is compelling evidence that improved, systematic stroke management, including rehabilitation, can reduce mortality and morbidity.[68,111] Rehabilitation comprises a broad array of biomedical, psychological, social, educational and vocational interventions that can be implemented in a variety of institutional and community-based settings. Services are often provided by a multidisciplinary team, whose composition depends on the patients' physical, cognitive and emotional impairments, as well as the availability of rehabilitation resources in the community.[37]

The main objective in stroke rehabilitation is to assist each patient in achieving the highest possible degree of individual physical and psychological performance. Rehabilitation has been described as the planned withdrawal of support, in which services are provided only when required.[96] The ultimate goal for many stroke patients is to achieve a level of functional independence that enables them to return home and reintegrate into community life as fully as possible. Stroke rehabilitation is often described as a process of active (motor) learning that starts, preferably, within the first few days after stroke. There is compelling evidence that organized stroke unit care, provided by a specialized stroke team (ie, expert care), is associated with reduced mortality, increased independency and more frequent discharges home.[68,111] Some trials found that this favourable outcome in ADL and independency is still significant at ten years post-stroke onset.[49]

It is currently unclear *why* the specialized stroke units are more effective than general medical units.[103] In general, there is no consensus as to when rehabilitation should start, what the optimum intensity is and how long it should continue. A number of factors have been claimed to contribute to the efficacy of care delivered in a stroke unit:

1) multidisciplinary communication on a regular basis[65];
2) better trained (skilled) staff providing more specialized care[38,50,65,124];
3) better organization of services and family integration[54,65–68];
4) earlier implementation of rehabilitation services and mobilization policies[4,38,39,50,65,106];
5) higher intensity of daily treatment[63,69];
6) more use of parenteral fluids, aspirin, antipyretics and antibiotics during the early phase of stroke rehabilitation[65,94].

Several factors have been found to differ significantly between a stroke unit and a general medical ward in favour of the former, such as pharmacological treatment (ie, increased prescription of heparin, intravenous saline and antipyretics), training of staff members (integrated nursing and physiotherapy) and earlier mobilization.[50,94] This latter finding suggests that successful rehabilitation depends upon the co-ordinated care of an expert multidisciplinary team in which a range of interacting factors contribute to the effectiveness of stroke rehabilitation units.[103,118]

In the last three decades, more than 300 randomized controlled trials (RCTs) have been published in the domain of stroke rehabilitation.[32] Most of these studies, however, had dissimilar objectives. As a consequence, these studies measured outcome in different ways, at different levels of impairment, activity and participation, and evaluated effects of interventions implemented at different times after stroke onset. In addition, most studies suffered from methodological shortcomings, such as a lack of blinding procedures and intention-to-treat analysis, which may have resulted in a positive bias in reported effects. On the other hand, several studies showed a lack of statistical power (type II error), reducing the likelihood of finding statistically significant differences. Nevertheless, a review of these studies shows two key elements that seem to determine the effectiveness of rehabilitation.

First, a number of randomized trials suggest that more therapy input results in better outcome. A meta-analysis of 20 studies involving 2,686 stroke patients suggested a beneficial effect of intensive therapy with regards to speed of recovery and perhaps the degree of recovery from hemiplegia and ADL independence.[129] In particular, those RCT studies that applied a treatment contrast between experimental and control groups extending beyond 16 hours seem to find a positive association with outcome in terms of ADL and instrumental ADL and a functional recovery mainly restricted to the lower limbs. This finding appears to be independent of the type of neurophysiological therapeutic approach applied[1,29,129] and can be explained mainly by the amount of additional therapy time used in the experimental group compared to the control group. Interestingly, the evidence for a dose-response relationship has also been found in two independent meta-analyses for the treatment of aphasia.[7,93] The most recent systematic review, involving eight adequately controlled trials[7], showed that the amount of therapy per week and the total amount of therapy were associated with enhanced performance.

Second, almost all studies performed so far show that therapeutic interventions are task-specific. In other words, their effects show hardly any generalization to other, often related tasks that are not directly trained in therapy.[60,119,120] For example, the application of motor re-education techniques, functional electrical stimulation and EMG (electromyographic) feedback therapy generates an improvement in muscular activation patterns, but these applications more or less fail to show any transfer of effects to other Activities of Daily Living (ADL). Limited generalization of treatment effects has been clearly demonstrated by Winstein and colleagues.[128] They showed that subjects who received standing balance training with a specially designed feedback device that provided dynamic visual information with regard to relative weight distribution over the paretic and non-paretic limbs attained significantly better static standing symmetry than those who did not receive augmented feedback. Despite these improvements in symmetry during stance, no generalization of these effects was found to control for the asymmetric limb movement patterns associated with hemiparetic locomotion.[128]

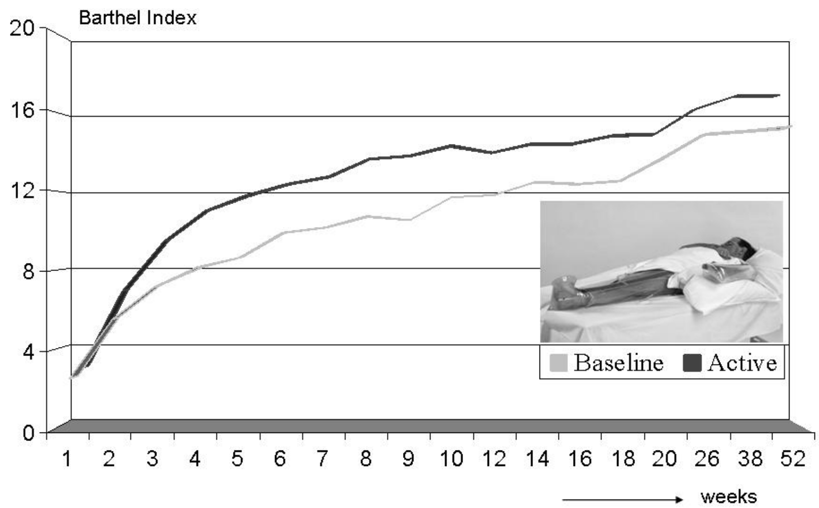
According to Wagenaar and Meyer[119,120] visual perception training in patients suffering from visual inattention constitutes an exception to this rule, showing some transfer of effects to reading and writing.[125] Only a few studies have demonstrated specific treatment effects at a functional (or disability) level, such as Cozean et al[17] for functional electrical stimulation in combination with EMG feedback therapy during sitting and walking; Shumway-Cook et al[102] and Winstein et al[128] for postural sway feedback therapy to improve balance in stance; Webster et al[125] for visual perception training during wheelchair navigation tasks; Powell et al[91] for electrical stimulation of wrist extensors in patients with some residual wrist extensor strength; Taub et al[114] for constraint induced movement therapy (CIMT) of the hemiplegic arm; and Hesse[46,47] for body weight supported treadmill training (BWSTT). [see ref.32,129 for a review]

The elements of intensity and task specificity that are considered to determine the effectiveness of therapeutic interventions have been integrated in newly developed interventions such as body-weight support treadmill training (BWSTT) and constraint induced movement therapy (CIMT). Both therapies are characterized by a forced use of the paretic limb in a functional manner. Recently, both elements (ie, augmentation and task specificity of treatment) were integrated in a randomized controlled study involving 101 patients with a primary middle cerebral artery (MCA) stroke.[59,62] All patients were assessed 18 times in the first year after stroke onset. Patients were allocated to one of three intervention arms. Subjects who received 30 minutes of additional training on every working day for 20 weeks showed faster improvements in gait in the group receiving lower limb rehabilitation in the experimental group, and faster recovery of dexterity in the group that received augmented upper limb rehabilitation, compared to the control group who were subjected to upper and lower paretic extremity air-splint immobilization (Fig. 1).

The effects were, however, only significant up to six months post-stroke, suggesting that active task specific training may merely accelerate functional recovery.

The long-term effects, however, remain unclear. A follow-up study showed that, on average, patients maintained the same level of activity up to one year after stroke. However, a significant number (ranging from 10 to 30%) of the patients showed further improvement or deterioration in functional outcomes such as gait speed, dexterity or ADL.[59] Unfortunately, it was not possible to predict which of these patients would change beyond the error threshold of measurement. However, patients with an incomplete functional recovery of upper or lower limb were most likely to change significantly.[59]

Fig. 1. Mean recovery patterns on the Barthel Index (n = 101) in patients immobilized by an air splint (grey curve) or receiving an active motor training programme focusing on lower limb function (black curve). No statistically significant differences were found at six months post-stroke, suggesting faster recovery for those who received more intensive rehabilitation in the first 20 weeks.[see refs. 59 and 62 for details] Inserted photo depicts a patient with air splint.



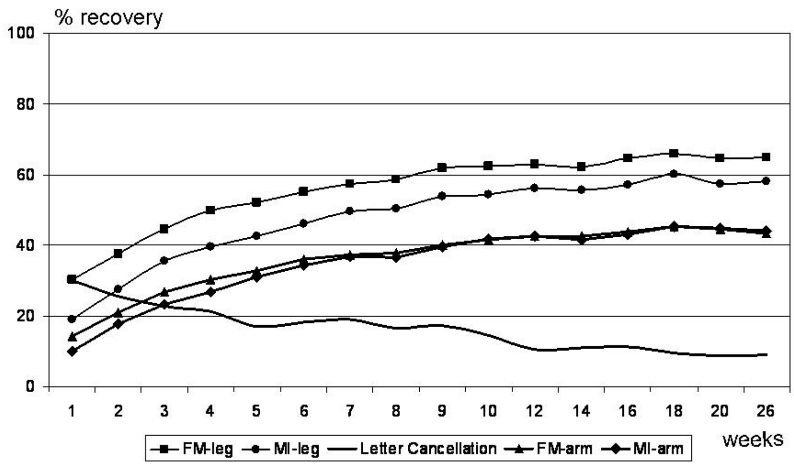
On the basis of this longitudinal study, three important issues should be addressed. First, the effects of rehabilitation may be temporary to a large extent and are more pronounced in the first six months post-stroke than later on (ie, in the chronic phase after six months post-stroke). Similarly, Ottenbacher and Janell, who reviewed 36 trials involving 3,717 patients, found a statistically significant negative association between effect sizes in individual trials, in terms of the effectiveness of rehabilitation, and the post-stroke timing of the first therapeutic intervention.[85] Their finding suggests that stroke rehabilitation has an optimal time window for obtaining favourable effects.[62] Second, the effects found are relatively small when compared to the substantial functional recovery often observed (about 10% of the variance in the outcome) and these effects occur largely irrespective of the type of therapy that is applied in the first six months post-stroke. For example, patients who received only a small amount of therapy, due to immobilization by means of an air-splint, showed almost the same, non-linear recovery pattern as a function of time as those who received lower or upper limb training (Fig. 1). In addition, identical exponential recovery curves were found for impairments after normalization of scaling properties such as strength, synergism and reduction of visual inattention as measured with the letter cancellation task and disabilities such as walking ability, dexterity of the paretic arm, balance and ADL (Fig. 2a and b). This suggests a common underlying mechanism of recovery that determines final outcome.

Third, the improvement in disabilities such as those of gait and dexterity, which are non-linearly related to underlying impairments like strength and synergism, can be partly explained by the use of behavioural adaptation strategies to compensate for existing deficits rather than only by restitution of the existing underlying impairments themselves.[64] Kinematic studies in particular have further elucidated the manner in which patients may improve their gait performance and dexterity by using behavioural compensation strategies.[64] For example, based on kinematic analysis of arm and leg swing in 53 hemiplegics, we showed that improvement in comfortable and increased gait speed after stroke resulted in a larger leg and arm swing on the non-paretic than on the paretic side.

This finding suggests that the contribution of the non-hemiplegic side to improvements in gait speed is larger than that of the hemiplegic side.[64] Similarly, Cirstea and Levin[16] showed that patients with severely to moderately impaired motor function of the upper limb are able to perform a reaching task by bending the trunk forward and controlling the reaching movement with the proximal musculature, thus compensating for their lack of motor control. These findings suggest that understanding the recovery of disabilities is far more complex than understanding the recovery of impairments alone.

Recent research findings reflecting compensatory movements, also relate to the long-standing discussion in rehabilitation medicine as to how patients with spastic hemiparesis should be approached for optimal results.[115]

Fig. 2. Mean normalized recovery patterns (% of maximum attainable recovery) for impairments such as Fugl-Meyer motor scores (synergism), motricity index scores of arm and leg (strength) and letter cancellation task (visual attention) as a function of time (n = 101); Mean normalized recovery patterns (% of maximum attainable recovery) for Barthel Index (BI), action research arm test (ARA), functional ambulation categories (FAC), trunk control test (TCT) and Fugl-Meyer balance test (FM balance) (n = 101).



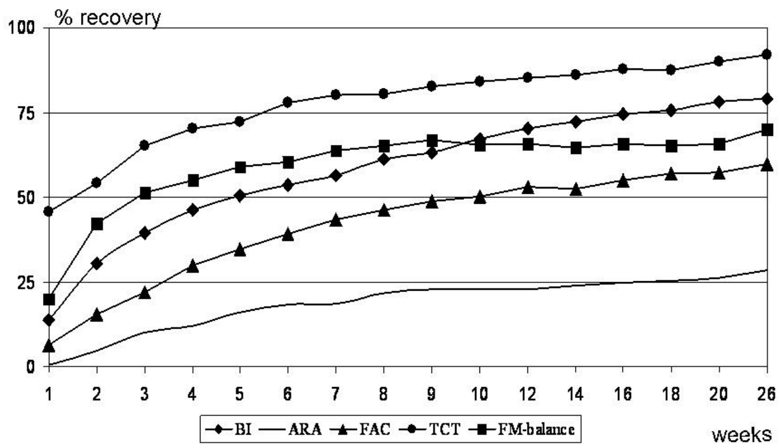


Figure 2 a and b

Although several approaches suggest that compensatory movements may potentially inhibit a return to normal neurological functioning and should be discouraged, evidence for this assumption is lacking. These remedial therapies, such as neurodevelopment treatment (NDT) or the Bobath approach, attempt to restore existing deficits, whereas other approaches, such as Brunnstrom, allow for compensatory movements. This may explain why more function-oriented compensatory therapies achieve their functional goals sooner than remedial therapies that do not allow for behavioural compensation.[60]

1.2 Understanding the pattern of functional recovery

Recent findings from several longitudinal studies suggest that, irrespective of the type and amount of therapy, the main pattern of recovery after stroke is determined by certain unknown biological processes, often characterized as 'spontaneous neurological recovery'.[36] The nature of this observed pattern of spontaneous neurological recovery is insufficiently understood. To date, surprisingly little clinical and experimental research has addressed the question why a certain degree of 'spontaneous' recovery is possible despite severe cerebral damage.[36,42] In rehabilitation medicine, spontaneous neurological recovery is perceived as one of the most neglected features of the clinical course of stroke[36 page 359] The reason for this omission is probably the lack of methods capable of measuring the effects of time on the course of recovery directly. One way of improving our understanding of the time course of recovery may be to proceed by investigating the factors that predict the pattern of functional recovery as a function of time.

Even though the outcome of stroke patients is heterogeneous by nature and individual recovery patterns differ, a strong mathematical regularity has been found in patients' functional recovery. For example, individual curve-fitting of time series of the Barthel Index (BI) in 89 stroke patients with a first-ever MCA stroke showed that the best fitting model to capture all time series in the first 26 weeks after stroke was a logistic regression model.[61, see also 121] In this model, A(t) represents the modelled recovery at time t, and Ap, C and K are constants that indicate different values for different patients (Fig. 3a). Ap is the modelled value of the final plateau, and C is the inflection point of the individual model curve at the time of fastest recovery (K) since onset. Analysis showed that the inclination of C was highly positively associated with Ap ($r_s = 0.69$; $p < 0.001$). In other words, patients showing greater improvements within the first weeks post-stroke reached higher plateaus at six months than those with later BI improvements (Fig. 3a). In addition, the time since onset for the fastest recovery (expressed as the number of weeks) showed a statistically significant negative association with Ap ($r_s = -0.47$; $p < 0.001$). This finding suggests that if recovery takes place early after stroke onset, better outcomes may be expected at six months post-stroke. Finally, regression analysis showed that the initial BI assessed in the first week post-stroke was the strongest predictor for the BI at six months, explaining about 56% of the variance in the outcome. In fact, the final outcome in terms of BI could be optimally predicted just by classifying stroke patients on the initial disability scale in the first week and adding 10 points (Fig. (3b)). Obviously, this suggests that the degree of recovery after MCA stroke is largely defined within the first weeks after the stroke, whereas after six months, further changes in functional recovery beyond the 95% CI of the error of measurement are restricted to about 10% of the stroke victims, in whom either further improvement or deterioration is found.[59] Apparently, the length of the period without improvement after the stroke, as well as the extent of improvement in the early stages after the stroke, reflect the intrinsic cerebral damage. Obviously, the time and extent of functional improvement since stroke onset determine the individual plateau phase from six months onwards.

The effect of time in relation to stroke outcome is further substantiated by the results of one of our recent studies, in which the effects of time since stroke onset were investigated with regard to the predictability of the outcome in terms of dexterity. This study included 102 first-ever, ischemic MCA stroke victims.[61] All patients were characterized by an initially flaccid arm in the first week after stroke. Subsequently, logistic regression analysis was applied for the prediction of the dexterity of the hemiplegic arm (using the action research arm test; ARAT) at six months post-stroke.

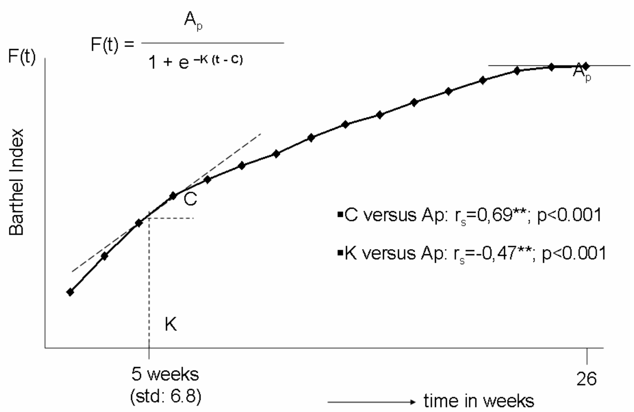
At six months, some dexterity in the paretic arm was found in 38% (> 9 points on ARAT) and complete functional recovery in 11.6% of the patients. Univariate analysis in the first week after stroke onset showed that the type of infarction (lacunar, partial or total hemispheric infarctions), right hemisphere stroke, homonymous hemianopia, visual gaze deficit, visual inattention and severity of paresis were statistically significantly associated with poor arm function. Surprisingly, the strongest determinant of the outcome in terms of dexterity was the severity of leg paresis in the first week.

Patients who showed some strength in the lower limb (≥ 25 points on the Motricity Index) had a probability of 74% of achieving some functional recovery (ARAT > 9 points) at six months, whereas the probability was only 14% for those patients who had a complete hemiplegia and failed to show any active movements in the lower limb (Fig. 4). When the candidate determinants were re-tested in the second week, however, the strongest determinant to emerge was the Fugl-Meyer (FM) arm score, followed by Motricity Index (MI) leg score. Patients with 11 points or more on the FM arm score and more than 25 points on the MI leg score had a probability of 89% of achieving dexterity at six months. Patients who failed to reach this level had only an 8% chance of regaining some dexterity.

In the fourth week post-stroke, the probability of developing some dexterity increased to 94% for those with sufficient recovery in the upper limb in terms of the FM arm score, but remained at about 6% for those who failed to achieve this level.

Interestingly, no change in the probability of improved dexterity was found after the fourth week, suggesting that the outcome in terms of dexterity is already defined within the first four weeks post-stroke and that lack of voluntary motor control of the leg in the first week with no emergence of arm synergies at four weeks is associated with poor outcome at six months.[61] Our results[61] are confirmed by a number of descriptive studies by Twitchell[116], Skilbeck et al[104], Heller et al[43] and Sunderland et al.[112] All these studies also found that the absence of a measurable grip function within about one month post-stroke indicates poor functional recovery of the hemiplegic arm.

Fig. 3. Functional recovery based on the Barthel Index (n = 89). A logistic function, which adequately fitted the individual recovery pattern, accounted for most of the variances found within the first 20 weeks post-stroke. F(t) represents the modelled recovery at time t; Ap, C and K are constants which have different values for different patients. Ap is the modelled value in the final plateau phase and C is the inflection point at the time of fastest recovery (K), while 'e' represents the natural logarithm. The mean moment of fastest recovery (K) is found at 5 weeks post-stroke (std. 6.8 weeks). K is found to be inversely related to final outcome Ap, while the amount of recovery on the BI at the time of fastest recovery (reflected by C) is positively related to the final plateau phase on the BI (ie, Ap); Mean recovery patterns classified according to the initial Barthel score (BI) (n = 89). Initial BI score, sitting balance (SB) and social support by a healthy partner predicted 56% of the variance of outcome at 26 weeks post-stroke. Further analysis showed that the time of fastest recovery within each patient group was highly associated with the initial BI score.



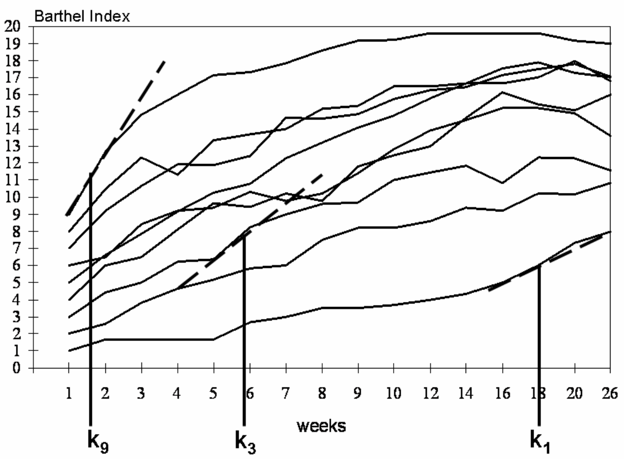
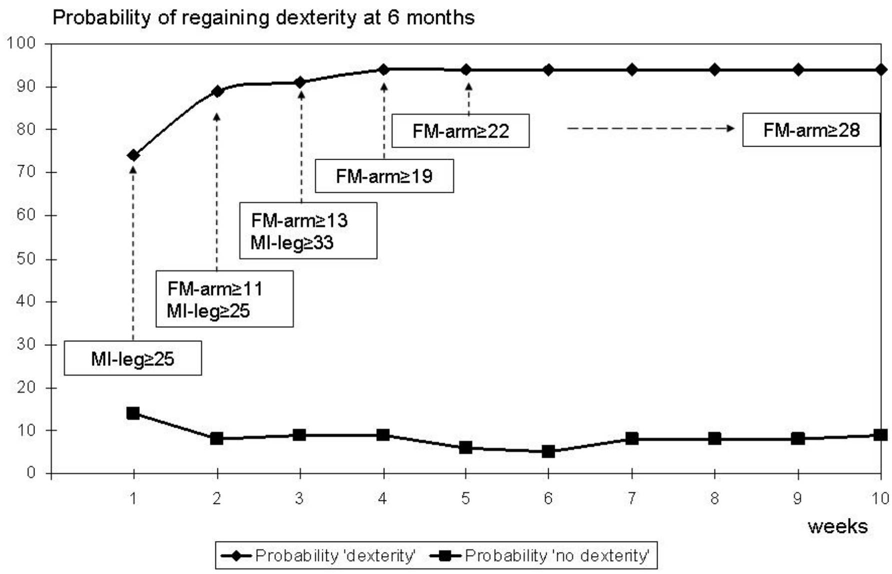


Figure 3a and 3b

Fig. 4. Probability (%) of achieving dexterity (ARAT ≥ 10) at 6 months post-stroke (n = 102). Based on the FM scores of the flaccid arm, optimal prediction of arm function outcome at 6 months could be made within 4 weeks after onset, whereas lack of voluntary motor control of the leg in the first week with no emergence of arm synergies at 4 weeks was associated with poor outcome at 6 months.[61]



This suggests that final outcome in stroke patients is largely determined within a limited time window. It should be noted, however, that after four weeks, motor strength and synergism still need to show further improvement in order to generate a favourable outcome (Fig. 4).

Obviously, the limited time window for the prediction of regaining dexterity after one month in relation to the effects of upper limb training treatment, such as neuromuscular stimulation[91] or exercise therapy[62,112], suggests that the differences in effects are restricted to those patients with some return of dexterity.

It is not without reason that some degree of willed extension of the wrist and fingers is often used as an inclusion criterion in upper limb trials, such as constraint-induced movement therapy, in order to select the patients that may be likely to improve functionally.[114] In line with this hypothesis, Platz and colleagues showed that 50% of the variance in motor improvement scores in patients with mild arm paresis who received arm ability training could be predicted on the basis of activation of sensorimotor areas during movement preparation and deactivation of other cortical areas during movement execution, as assessed with multi-modal EEG.[90]

The processes taking place within this critical time window of four weeks post-stroke probably reflect the area of brain tissue that is irreversibly damaged by ischemia, as opposed to those areas that are potentially able to recover. The challenge to the rehabilitation scientist is to improve the understanding of the various mechanisms that are involved and define the restricted time window for the outcome of functional recovery after stroke. Improved understanding of these processes would enable clinicians to define the optimal treatment goals within an individually tailored treatment programme and to develop new therapies that specifically interact with the processes of recovery, such as pharmacological agents that may enhance the effectiveness of training.[62,107]

1.3 What are the mechanisms of functional recovery?

A number of mechanisms that have been hypothesized in the literature may contribute to the predictability of the process of functional recovery after stroke. In the past, the mechanisms underlying neurobehavioural recovery from lesions in the central nervous system such as stroke have been extensively described by Luria. These mechanisms are often described as involving either restitution or substitution of function.[97]

The restitution model suggests that the lesioned area recovers as a result of tissue repair, while its function is assumed by other cortical and subcortical structures, either adjacent to or remote from the damaged area. This theory is known as 'vicariation of function' .[83,117] Understanding the theory of vicariation of function requires an appreciation of several short-term and long-term physiological processes, such as the unmasking of previously present but functionally inactive connections, axonal and dendritic regeneration (ie, collateral sprouting), synaptogenesis and denervation hypersensitivity.

Based on these mechanisms of repair, Von Monakow[117] hypothesized at the beginning of the 20th century that neurological recovery is largely due to a reactivation of functionally suppressed areas remote from, but connected to, the area of primary injury. This process is known as resolution of diaschisis.[30, 83,100,117] Recent PET scan studies showed that immediately after an acute stroke, restitution of non-infarcted penumbral areas around the infarcted area, ie, resorption of extracellular and intracellular oedema and necrotic tissue by reperfusion of viable areas, may contribute to spontaneous functional recovery in the early stages after stroke.[100] The substitution model, by contrast, suggests that functional recovery after stroke occurs largely by behavioural compensation, by which patients learn to compensate for their acquired deficits.[83,97] There are currently strong indications that both phenomena, ie, restitution as well as substitution, are largely responsible for the functional improvement observed after stroke. The various mechanisms potentially involved in functional recovery are discussed in the next four subsections.

1) Restitution of non-infarcted penumbral areas

The hypothesis of the restitution of non-infarcted penumbral areas assumes that the affected cerebral tissue has just enough energy to survive for a short period of time but not enough to communicate and function. As the neurons in the penumbra are still structurally intact and capable of re-functioning, they are believed to intervene in the acute phase in order to limit the infracted area. In particular, the introduction of Positron Emission Tomography (PET) and diffusion-perfusion Magnetic Resonance Imaging (MRI) in cerebrovascular disorders has been accompanied by a rekindling of interest in human brain function and the clinical pathophysiology of cerebral ischemia, as well as in the restoration of function within penumbral areas by reperfusion.

Due to the absence of a universally accepted definition of the penumbra, different concepts have emerged in the literature. Ischemic penumbral tissue is often described as the region that surrounds a severely hypo-perfused centre (ie, the ischemic core), in which electrical failure has occurred, but membrane homeostasis is maintained.[87] In view of the dependence of homeostasis on the

ATP pump, the status of penumbral tissue after arterial occlusion is presumed to be directly related to the level of oxygen preservation, which in turn depends upon a patent regional cerebral blood flow (rCBF). The location and extent of the penumbral area depend largely on factors such as the time elapsed since occlusion and the severity of the ischemia. It is believed that some peri-infarcted hypoxic tissue may elude Wallerian degeneration and regain its function if reperfusion occurs.

Although the presence of a non-infarcted penumbral zone in the acute ischemic state has been well established, and constitutes the main target for most acute medical interventions applied within 3 to 6 hours post-stroke onset, there is not much evidence that the non-infarcted penumbral tissue remains viable for a prolonged period of time after vessel occlusion.[6,34,70,77] For example, Phan et al[87] reported that expansion of the ischemic lesion from viable into infracted tissue may occur within the first hours and in some patients for some time after this period. In particular, the large percentage of variance explained by derived prediction models immediately after stroke onset suggests that the outcome is largely defined at this stage of events, often captured in the first assessment. This finding suggests that the location and extent of the area of irreversible cell damage (ischemic core) should be highly predictive of the functional loss after six months.[see e.g. 61] In particular, the cerebral metabolic rate for oxygen ($CMRO_2$) in PET is considered to be a reliable parameter for assessing irreversible tissue damage. This hypothesis has gained acceptance with the findings of Marchal and colleagues[77], who measured O-PET[15] and showed that irreversible tissue damage was largely defined within 5–18 hours after the onset of a first-ever MCA stroke. They found that if voxel values of cerebral blood flow (CBF) were below 8.43 ml/100 ml/min and if the oxygen consumption of $CMRO_2$ was below 0.87 ml/100 ml/min, the brain parenchyma was irreversibly damaged. In addition, they showed that the percentage of irreversible tissue damage calculated from all voxels in the involved hemisphere relative to the non-involved hemisphere was significantly and positively correlated to both the final volume of the infarct and the outcome at two months ($r^2 = 0,69$; $p < 0.001$).[77]

In agreement with a limited therapeutic time window for reperfusion, most studies have shown that almost 90% of the initially non-infarcted penumbral tissue becomes infarcted within three hours post-stroke.[6,34, 57,77] In some cases, however, tissue may still be saved from infarction for up to 16 or even 42 hours after stroke onset.[6,31,77,87] These findings suggest that the ischemic penumbra surrounding a focal cerebral lesion can be regarded as salvageable if reperfusion occurs in time.[87] Theoretically, reperfusion may be a mechanism for neurological recovery and as such present a plausible explanation for the spontaneous recovery found during the first days after stroke onset.
However, reports pertaining to the process of salvage and restoration of ATP function after reperfusion are scarce. In any case, the limited time window of several hours for eluding irreversible cerebral tissue damage after arterial occlusion is difficult to match with the long-term recovery pattern observed even beyond the first six months post-stroke.

2) Resolution of diaschisis
A second, much less investigated mechanism potentially responsible for more extensive early recovery after stroke may be the occurrence of diaschisis and its resolution. Von Monakow[117] asserted that the function of brain areas remote from, but anatomically connected to, the infarcted area is depressed due to an interrupted functional input from the injured region.[117] Contrary to slow-growing lesions (e.g. tumours), acute lesions as a result of stroke or cerebral trauma are known to result in such reactive depressions.
A number of studies have provided evidence for the existence of a so-called 'apoplectic shock', which relates to reduced metabolism and regional cerebral blood flow (rCBF) in functionally related areas of the brain after stroke.[2,30,83,100,117]
There are strong indications that, immediately after stroke, cortical injury results in hypometabolism and inhibition of areas remote from the infarcted area (cerebral shock). The down regulation of neural activity is considered to be due to a glutamate-mediated toxicity which results in destabilization of N-Methyl-D aspartate (NMDA) receptors, with a subsequent influx of Ca^{2+} and Na^{+} ions. In

addition, a decrease in afferent input received from the area of infarction may contribute to the suppression. Diaschisis has been described as the mechanism responsible for the inhibition of the cerebellar hemisphere contralateral to a supratentorial spinal tract injury.[113] Recent small focal stroke models with PET in rats show that the anatomically and functionally related cortical areas with hypometabolism may be more than 13 times larger than the infarcted area itself.[15] Decrements in glucose metabolism are assumed to reflect synaptic activity and hence the disruption of normal glial–neuronal relationship in these adjacent cortical areas.[15] Recovery is believed to occur as a result of the gradual reversal of this functional suppression of viable neuronal tissue. It is important to note that diaschisis should be distinguished from irreversible brain damage and could be a possible explanation for the more extensive loss of function that occurs immediately after stroke onset.

A number of reports suggest that recovery of, for example, dexterity after stroke may be caused by adaptations taking place in corresponding cortical motor maps of the involved but also of the non-involved hemisphere.[2,13] Recent studies of brain metabolism after cortical injury have largely confirmed that resolution of diaschisis is likely to play an important role in these processes of cerebral recovery.[83,100,117] For example, a number of studies have demonstrated the compensatory abilities of the ipsilateral hemisphere following an initial suppression immediately after stroke onset.

The initial suppression (so called 'diaschisis commissuralis'), transmitted via axons of the corpus callosum from related areas in the ipsilateral hemisphere[117], may be one of the possible mechanisms responsible for the more than expected extensive functional loss at onset based on the involved area of irreversible cerebral damage involved. Studies investigating rCBF with PET scanning have demonstrated the occurrence of a short period of 'transhemispheric depression of metabolism' after ischemic infarction.[48,73] For example, Weiller et al[126,127] showed a significant increment in rCBF within the contralateral posterior cingulate, premotor cortices, and within the ipsilateral caudate nucleus in ten patients who were recovering from a lacunar striatocapsular motor stroke. The activity in these areas was more pronounced than in normal subjects. However, different individual patterns of organizational and functional compensation were found, depending on the site of subcortical lesion and the motor somatotopy of the pyramidal tract.[126,127] Similar findings have been reported by Pantano et al[86] in chronic stroke patients (n = 37) enrolled in the study at 3.6 (±1.6) months after stroke onset. Measurements of the rCBF of the ipsilateral hemisphere (ie, nucleus caudatus, thalamus, lentiform nucleus and premotor cortex) were positively correlated with the improvements observed during the three months of the study.[86] Finally, Seitz and colleagues, using PET scanning in recovered patients who were able to perform sequential finger movements with the recovered hand after six months showed a recovery related network remote from the stroke lesion.[100] This network was characterized by a topographic overlap with the lesion-affected network, suggesting that diaschisis may be a key factor in the process of stroke recovery.[100]

It should be noted that diaschisis is not restricted to the hemispheres themselves, but involves the spinal cord and contralateral cerebellum as well. This neural structure is able to compensate for the functional depression resulting from motor cortex injury. For example, immediately after stroke onset, depression of the pyramidal tract fibres within the spinal cord may result in flaccidity. This mechanism has been described by von Monakow[117] as 'diaschisis corticospinalis' and is comparable to the phenomenon of 'cerebral shock', which is often seen in severe stroke patients.[5,30,83,117] The underlying mechanism of spinal shock is unknown, but it may be the result of a transient loss of descending excitatory input, resulting in hyperpolarization of alpha motor neurons.[117,127] The ability of the spinal cord to compensate for the imposed inhibition after stroke has already been described by Twitchell[116], who found a recurrence of myotatic stretch reflexes within 48 hours, followed by a gradual return of muscle tone. The increasing muscle tone allows the emergence of stereotypic movement patterns (ie, synergies), which basically enables the stroke patient to stand upright and walk.

The above findings suggest that the discontinuation and compensation of functionally depressed areas may be the result of another neurophysiological mechanism underlying the non-linear process of ‘spontaneous neurological recovery’ after stroke.

3) Tissue repair

A third mechanism that may contribute to the nonlinear recovery pattern is brain plasticity caused by anatomical and functional reorganization of the CNS, such as synaptic sprouting, functional enforcement in existing neural circuits (ie, unmasking) and development of fresh polysynaptic connections.[83,99,110] The changes in cerebral properties may be expressed at two interacting functional levels of the nervous system: at the level of sensory and/or motor representation of the cortex (ie, map plasticity) and at a neuronal level (ie, neuronal or synaptic plasticity).[9] Two other neural mechanisms of recovery that are closely related to mechanisms of sprouting are the processes of unmasking of existing but functionally inactive pathways and the use of alternative functional pathways that involve the normal system of cerebral circuit redundancy.[72] The time window during which different forms of plasticity occur is wide and may not be restricted. Short-term changes within minutes are probably due to unmasking of latent synapses involving modulation of GABAergic inhibition, whereas long term changes involve mechanisms in addition to the unmasking of latent synapses such as axonal regeneration and sprouting with changes in the shape, number, size and type of synapses. There are strong indications that training may enhance these plastic mechanisms. There is now considerable evidence to support the view that the adult human brain maintains the ability to reorganize itself throughout life. This ability may underlie the capacities to learn and to recover from injury. Consistent with findings from RCTs in stroke rehabilitation, there is strong evidence from recent animal studies that elements of intensity (ie, the number of repetitions) and specificity of training also impact upon the extent of use-dependent cortical plasticity.[11,83] These elements are similar in animals and humans.[76]

However, the concept of cerebral plasticity is poorly defined in the literature. The present review uses the term ‘plasticity’ according to the definition used by Bloedel et al[8 page 440] and Boroojerdi et al[9] as ‘any enduring change in cortical

properties either morphological of functional'. Plasticity generated by anatomical and functional reorganization is often characterized as one of the unspecified mechanisms that may be responsible for resolution of diaschisis and with that alterations to cortical or subcortical maps.[2,15,30] For example, after disruption of the pyramidal pathway, Asanuma[3] showed increased activity in adjacent areas of the motor cortex. This finding suggests that cortical maps adjoining the locus of injury within the involved hemisphere are able to adapt to the functional loss. Apparently, the somatotopic representations of the cortex should not be regarded as a static array of hard-wired parallel circuits, but rather as a dynamic system which is capable of reorganizing (within hours) its somatotopic representation.[8] Although evidence for the reorganization of cortical maps in associated areas after stroke is limited, a number of studies have demonstrated a shifting of cortical maps after digit amputation[79], somatosensory deafferentiation[80] and motor nerve lesions[27] in the mammalian brain, a process enhanced by (motor) learning. There is also evidence that the cortex adjacent to affected and nonaffected areas within the cerebral hemispheres mediating stroke recovery assumes the function of deactivated pathways. For example, Weiler and colleagues showed that in patients with lesions limited to the posterior limb of the internal capsule, recovered hand movements led to motor cortex activation that extended laterally to the face area, suggesting that the hand representation shifts toward the face area.[127] In addition, a number of authors have raised the possibility that the ipsilateral motor pathways also play a role in functional recovery.[72,127] Several published case studies have described a re-appearance of hemiplegia on the recovered side after a second stroke in the ipsilateral hemisphere, suggesting a 'take-over' of ipsilateral motor pathways.[72]
Learning-dependent synaptogenesis has been shown to occur in rats trained to perform a skilled reaching task. This training led to an increase in the number of synapses per neuron within layer V in the caudal forelimb area.[58,92] However, the rostral forelimb areas failed to show such cortical reorganization.[58,92] Skill learning is also accompanied by an increased horizontal synaptic density within layer II/III of the motor cortex. At least in the barrel cortex of rats, modification

of local N-methyl-D-aspartic acid (NMDA) receptors is necessary for the development of experience dependent plasticity.[84,92]
Finally, an increment in growth-associated proteins (GAP) and synaptophysin proteins has been found in the mammalian brain, providing evidence for the occurrence of sprouting in neocortical structures.[110] It should be noted, however, that plasticity is not identical to anatomical tissue repair in the sense of 'several axons crossing damaged neocortical brain areas'.[27,53]
Furthermore, the concepts of diaschisis and anatomical tissue repair are not mutually exclusive. For example, the restitution of function by tissue repair (ie, processes such as denervation supersensitivity, sprouting and synaptogenesis, as well as 'unmasking' of previously unused dendritic and synaptic pathways) may be regarded as mechanisms by which the brain operationalizes processes such as deactivation and reorganization of cortical or subcortical maps. Therefore, deactivation of diaschisis is often seen as an expression of plasticity which compensates for the primary injury.
It is believed to resolve over time and to be responsive to environmental stimulation and to the action of monamine agonists such as alpha receptor agonists.[2,30] Thus, cortical plasticity appears to play a beneficial and adaptive role in the recovery from stroke, but it should also be noted that not all plasticity results in beneficial effects in terms of impairments and activities.
There are several examples of morphological and functional changes (plasticity) in the central nervous system being negatively associated with recovery after stroke. These include epileptic seizures after stroke and the gradual development of hyperreflexia and clonus, which are regarded as positive symptoms of spasticity. In other words, neuronal plasticity and functional reorganization of the nervous system are not synonymous but closely related to each other.

4) Behavioural compensation

Finally, there are strong indications that motor recovery after cortical injury occurs to a large extent through behavioural compensation, rather than via processes of 'true recovery' alone. In fact, behavioural compensation strategies are considered to be potential confounders in our understanding of 'neural repair' and related cerebral recovery after stroke.[101] For example, in one recent study of stroke patients, moderately to severely impaired subjects used compensatory strategies of the trunk to accomplish a pointing task, rather than trying to achieve restitution of the original arm function.[16] These findings are in agreement with a recent longitudinal study which found that patients tend to compensate for the loss of isolated hand and elbow movements by securing the elbow in a flexion synergy position when performing a reaching task of the hemiplegic arm after stroke.[109] Apparently, patients prefer to control the movement proximally at the trunk and shoulder, while simultaneously freezing the elbow, wrist and hand in a pre-adjusted mid-position during the transport phase of the reaching task.[16,109]

The manner in which patients try to control functional movements after stroke, such as during gait and reaching, is in agreement with Bernstein's theories of human movement behaviour.[71] According to Bernstein, the most fundamental solution to the problem of controlling co-ordination consists of reducing the number of independent elements to be controlled. In other words, locking the elbow in a synergistic pattern enables the patient to compensate for the weakness of the paretic elbow musculature. Obviously, the synergy dependent grasp with the upper limb may be seen as an adaptive mechanism that facilitates functionality by (1) reducing the degrees of freedom and hence the complexity of movement control and (2) compensating for the muscle weakness at the distal extremity that can be controlled for less accurately.[71,109] Apparently, the central nervous system strives to solve the lack of movement co-ordination by reducing the number of free to-be-controlled elements of the movement system. Advantages to selecting this more simple strategy of movement control may be found in the reduced energy costs required to achieve the goal of movement, as well as higher accuracy in controlling the movement despite existing constraints like weakness, increased stiffness due to spasticity and decreased perception.[109]

Recently, compensation strategies have also been found in the lower limb of patients who improved walking speed after stroke.[64] This study showed that increasing walking speed resulted in relatively larger increments in step and stride length on the non-paretic side compared to the paretic side. In other words, the compensating contribution of the non-hemiplegic side of the body to increased walking speed by alternating arm and leg swing was found to be larger than the contribution of the hemiplegic side of the body.[64] Obviously, one may conclude that functional recovery is not only a matter of restoration or restitution, but also a matter of compensation by using alternative movement strategies to achieve the intended goal.[101] Moreover, normal motor behaviour of healthy subjects may not serve as a measure of reference for understanding the adaptive motor behaviour of hemiparetic stroke patients.[71]

The compensating movement strategies are not captured by merely measuring impairments, such as motor strength, synergism and perception. Likewise, measurements at disability level can not differentiate between improvements at impairment level and the use of alternative movement strategies. Therefore, in an attempt to create an overall picture of the changes that occur after stroke, there is consensus among rehabilitation scientists about using a range of measurements when exploring outcomes of transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI).[28,122]

A better understanding of the relationship between the mechanisms of cortical reorganization and recovery from impairments and disabilities, including the existence of behavioural techniques to compensate for existing deficits, may have a major impact on the timing and content of rehabilitation-oriented and pharmacological therapies. Moreover, it would facilitate the interpretation of the development of the synergy dependent compensatory movements often observed during recovery after stroke.[116] A better understanding of the bi-hemispheric plasticity after stroke would also allow for the development of new therapies that attempt to enhance plasticity. However, for a better interpretation of above findings the interaction between plasticity processes after stroke and functional recovery requires further elucidation. Obviously, longitudinal studies are needed to investigate the impact of impairments and kinematic changes on functional outcome over time observing patients from the first days post-stroke onwards.

1.4 How are changes in cortical activation patterns related to functional improvements of the upper limb?

The significance of the changing task-related cortical activation patterns found after stroke for the recovery of abilities is insufficiently understood, and conflicting results have been reported in the literature. In particular, the use of fMRI[78; see for a review: 45] and TMS[76,44,75] as non-invasive techniques facilitates studies to be continued on the impact of the changing cortical activation patterns on improving motor functions after stroke. Both methods support the concept that neuronal reorganization (ie, neuroplasticity) in the affected and non-affected hemispheres contributes to functional recovery after stroke. However, most studies have investigated the impact of changes in motor function on fMRI cross-sectionally by comparing fMRIs of healthy age-matched subjects.[13,18–25,52,55,56,82,88,89,130] Unfortunately, few studies have directly related the macroscopic plastic changes in cortical activation patterns of stroke victims, as revealed by fMRI or TMS, to the process of recovery of functional abilities. In addition, most studies choose the time since onset of fMRI arbitrarily. As a consequence, the interpretation of any association between the fMRI image and improvements observed in functional recovery becomes subject to speculation.[see also critical comments in 26] For example, in most studies it is unclear whether activation of the ipsilateral motor cortex with movement of the recovered hand[127] represents true involvement of the ipsilateral motor pathways or merely reflects unwilled mirror movements of the unaffected hand due to lack of transhemispheric GABAergic inhibition. Although there is little doubt that recovery from stroke involves plastic reorganization of the brain, the challenge is to identify which of the many changes demonstrated are important in mediating functional recovery after stroke.

Understanding the dynamic process of functional recovery and overcoming the problem of heterogeneity of fMRI findings between subjects require longitudinal studies.[123] To date, eleven longitudinal studies have used fMRI to investigate the dynamics of motor recovery of the upper limb after stroke. In these studies, patients were scanned within a few days as well as several months after stroke onset. Six studies restricted their investigation to the first six months following ischemic stroke[31,78,98,105,108,122], whereas four reported the effects of stroke rehabilitation in the chronic stage.[14,51,74,78] All fMRI studies examined recovery of the paretic arm[31] and/or hand function[18–25,31,51,52,55,78,82,88,89,95,105,108,122,130] as a function of time. In these studies inclusion was confined to patients suffering from ischemic stroke only, with the exception of the studies by Levy et al[74] and Staines et al[108], which also included patients with hemorrhagic strokes. Almost all studies investigated only patients with good or excellent motor recovery of the hand after stroke, based on their ability to perform a finger-tapping or finger-to-thumb opposition movement. These studies reported task-related brain activation in patients mainly in the contralateral sensorimotor cortex[31,78,105,108], contralateral premotor cortex[31,78,108], ipsilesional cerebellum[105] and bilateral supplementary motor areas (SMA).[31,78,105,108]

In general, two main patterns of neural reorganization have been found during motor recovery of hand function after stroke. In the affected (infarcted) hemisphere, a predominantly posterior and lateral shift of cortical activation has been observed on fMRI[14,122,127], whereas the non-affected hemisphere showed increased activity levels suggesting an initial migration of the activation away from the affected hemisphere.[127]

These studies have often reported task-related brain activation in the bilaterally supplementary motor area and parietal cortex, the ipsilesional cerebellum[105] and the ipsilateral (non-lesioned) sensorimotor and premotor cortex.[31,108,122]

However, the clinical significance of these ipsilesional and contralesional shifts and increase of activation remains unclear. It is often assumed that these cortical increments are associated with rapid motor recovery, reflecting a 'takeover' of the damaged area.[76,108,127] Only a few studies employed an array of measurements to acquire a better understanding of the impact of the reported changes at the impairment as well as disability level.[see also comments in 122,123] None of the longitudinal studies investigated the process of impact of plasticity on outcome by controlling for the kinematic changes during functional improvement. As a result, these studies failed to differentiate between 'true motor recovery' and 'compensatory motor recovery'. This causes considerable difficulty in the interpretation of these changes in fMRI studies, apart from other potentially confounding factors such as a lack of control for mirror movements, strength, precision and the timing of imaginary movements (motor paradigm) during fMRI scanning[see also critical comments in 26]

Recently, there have been indications that this shift from the affected to the unaffected hemisphere is strongly dependent on the severity of the stroke and the integrity of the corticospinal tract system.[31,78,105, 122,123] Longitudinal studies have shown that after an early increase in task-related brain activation, improved motor recovery of the upper limb is accompanied by a reduced cortical activation pattern on fMRI in motor-related regions such as the bilateral sensorimotor cortex, premotor cortex, SMA, cingulated motor areas and cerebellum.[12,78,122] The use of fMRI in patients who failed to show (incomplete) functional recovery due to irreversible damage of the corticospinal tract of the hand demonstrated an increment and shift in cortical activation patterns.[31,78,122,123] For example, Feydy and colleagues conducted a longitudinal analysis of three successive fMRIs in 14 stroke patients and showed that only extensive injury due to Wallerian degeneration (as shown by TMS) in the primary motor areas of the hand (M1) resulted in an ipsilateral recruitment of activity within the hand area in the non-involved hemisphere in 3 out of 4 cases.[31] Patients in whom the primary motor area was spared or partially damaged showed a restricted pattern of activation towards the involved motor cortex only, without recruitment of ipsilateral areas (8 out 10 cases). The findings of Feydy et al suggest that ipsilateral recruitment of the non-involved hemisphere after stroke can be regarded as a compensatory cortico-cortical process, which is primarily related to the severity and location of the lesion in the primary cortex of the hand (M1).[31] These findings are confirmed by the results of a recent study by Zemke and colleagues.[130] They showed a 2.7 fold larger contralateral ventral sensorimotor cortex activation pattern in stroke patients with full motor recovery, despite similar tapping force, frequency, range of motion and electromyogram, compared to partially recovered patients. In addition, smaller ipsilateral premotor and larger contralateral sensorimotor activation patterns

were found in patients with right arm involvement compared to those with left arm involvement.
Obviously, the longitudinal studies suggest that ipsilateral recruitment of the non-involved hemisphere after stroke may be regarded as a compensatory corticocortical process, which is mainly inversely related to the severity of the lesion of the primary cortex of the hand (M1) (ie, more extensive lesions with concomitant poorer recovery of dexterity are accompanied by larger ipsilateral activation patterns). This hypothesis fits in with studies in primates with experimental lesions that demonstrate that when the corticospinal tract (M1) is preserved, motor recovery proceeds by reacquisition of pre-infarct movements. In contrast, irreversibly damaged cortical areas show the development of compensatory movement patterns.[33] Also, stroke patients showing involvement of corticofugal motor efferents are less likely to recover from impaired upper limb function.[101] On the other hand, interhemispheric disinhibition will be prevented in less severely M1 injured patients, in whom some elements of the corticospinal tract have been preserved, and functional repair will be directed towards restitution of the original functionally intact corticospinal neurons of M1. For example, Friel and Nudo showed that the amount of recovery of skilled hand use in adult squirrel monkeys after a small ischemic infarct of the hand area (M1) was related to the relative size of the lesion and its specific location within the M1 hand representation.[33]
Consistent with these longitudinal fMRI studies are the findings of Ward and colleagues who recently showed a negative association between functional outcome in terms of dexterity and task-related cortical activation patterns. They cross-sectionally investigated 20 patients with variable degrees of recovery at least three months after stroke onset and found that poor functional outcome was significantly negatively correlated to increased task-related activation patterns within the bilateral or ipsilateral dorsolateral premotor cortex, cingulated sulcus, contralateral SMA and pre-SMA, contralateral insular cortex and bilateral cerebellar hemispheres and vermis. These findings suggest that bilateral recruitment of these regions occurs in patients with poor outcome, but not in those with good outcome in terms of dexterity.[123] The regions that are

bilaterally activated involve the sensorimotor, premotor, posterior parietal, prefrontal and insular cortices, SMA, cingulated motor areas (CMA) and cerebellum.

Obviously, if the corticospinal input from M1 is preserved, less reliance is needed on using parallel motor areas to generate an alternative input. However, because of the nature of these alternative projections[10], functional recovery is usually incomplete or absent.[31,101,123] Unfortunately, such a negative association between preservation of the corticospinal tract to the hand (M1 neurons), suggesting focussing of brain activation on fMRI[31,78] and PET[129], could not be confirmed by Ward and colleagues.[122] Although they also found a reduction in task-dependent activation over time after stroke, they were not able to associate this decrement with the initial severity or rate of recovery in the eight stroke patients involved.[122] On the other hand, the hypothesis that task-dependent focussing of cortical activation depends on the integrity of corticospinal projections to the hand is consistent with studies of the predictive value of early TMS.[40–42] Therefore, it may be hypothesized that ipsilateral activation of parallel corticospinal tract neurons (M1) is insufficient and at best helpful in supporting the activation of synergistic proximal arm and trunk muscles.

It does not assume the function of the muscles of the paretic hand. In addition, rather than projecting to the ipsilateral muscles of the hand, anatomical studies in humans show that the ipsilateral corticospinal connections mainly end in axial and proximal stabilizing muscles.[10] It may even be hypothesized that the increment of ipsilateral cortical maps after unilateral stroke may be regarded as a (temporary) release phenomenon, due to transhemispheric disinhibition of GABA neurons[35,70], which is often observed in patients with large strokes and poor motor recovery.[30,35]

Thus, the functional impact of changes in ipsilateral and contralateral activation patterns on fMRI as a reflection of plasticity needs to be re-examined. There is now growing evidence that the strategy of motor remapping after injury of the primary motor cortex of the hand (M1) as a result of a middle cerebral artery stroke will depend greatly on the integrity of the corticospinal tract itself (ie, the severity of Wallerian degeneration) early after stroke onset. It has been found that for patients with severe M1 lesions, the optimal strategy to compensate for the (irreversible) loss of dexterity is to recruit the corresponding ipsilateral areas of the non-involved hemisphere. Correspondingly, it may be hypothesized that behavioural compensation strategies are more likely to be related to an insufficient return of neural function within the original brain areas (M1, SMA and PMA) in the contralateral hemisphere than to a real 'take-over' of neural function by (ipsilateral) cortical activations. Patients showing reversible, partial loss of dexterity, however, show a shift in activity to the original brain areas within the M1, reflecting brain activity which is comparable to what is found in healthy subjects.

1.5 Conclusions and implications for future studies

In the last three decades, a number of studies have shown that augmented task-oriented training may enhance the processes of functional recovery after stroke. In particular, therapies that combine the elements of intensity and task specificity, such as constraint induced movement therapy (CIMT) and body-weight supported treadmill training (BWSTT) have been found to be most effective. On the other hand, a number of cohort studies have shown that the outcome of functional abilities such as dexterity is highly predictable early after stroke and that the time since stroke onset is an important factor determining the accuracy of prediction. Although there is now strong evidence that task-oriented rehabilitation programmes may facilitate this natural pattern of recovery, their impact is relatively small when compared with the predictable recovery course observed in the first six months post-stroke. Why intensive task oriented rehabilitation programmes applied at an early stage influence this natural course of functional recovery is not known. For this reason, a better understanding is needed of mechanisms that may contribute to the process of functional recovery after stroke. Mechanisms claimed to be responsible for the non-linear change over time include recovery of penumbral tissue around the infarcted area, subcortical reorganization, reduction of temporarily deactivated intact brain remote from, but anatomically connected to the area of the primary injury, reinforcement of ipsilateral motor pathways and behavioural compensation strategies.

Non-invasive imaging techniques such as fMRI and TMS in particular have shown that changes in activation patterns in the ipsilateral and contralateral brain structures, such as the thalamus, caudate and lentiform nuclei and prefrontal cortex, are enhanced by rehabilitation and parallel functional recovery. Currently, the plastic cerebral changes reflecting neuronal reorganization are often regarded as important mechanisms explaining the functional recovery after stroke. However, the interpretation of fMRI, PET[81] and TMS changes relating to neuronal reorganization and functional repair is still inconclusive and not unequivocal. Besides clinical heterogeneity due to differences in timing post-stroke and severity of deficits, other factors hampering comparisons between studies include differences in the motor paradigm and the assessment of impairments and disabilities as well as differences in the techniques used to assess brain activity. In addition, only a few fMRI studies have related these dynamic changes in cortical activation (re-mapping) to neurological improvements in a longitudinal design, whereas those studies that investigated stroke patients longitudinally failed to observe the impact of changes in cortical activation in a functional approach.

The interpretation of fMRI findings is further complicated by our lack of understanding of the concept of 'motor recovery'. In other words, it remains unknown what is improving in the motor control in patients demonstrating functional recovery. This phenomenon requires a better understanding of the 'nature' of co-ordination deficits in functional tasks, and thus of the natural and physical laws of co-ordination and control in the performance of such tasks. In this context, it is obvious that the emergence of synergistic movement patterns, as well as the concomitant changes within the motor system, such as increased stiffness, will both lead to altered motor control. From the perspective of Bernstein's law of motor control, however, these changes, which are characterized by reduced joint involvement in the paretic limb, proximal motor control and uncoupling of successive joint movements, may be regarded as adaptive behaviour. After all, these changes enable patients to control functional tasks with more accuracy and less energy by reducing the number of degrees of freedom. It may thus be hypothesized that the preferred motor pattern in which hemiplegic patients move may be viewed as the optimal adaptive behaviour for a given state of the system of movement production, rather than as a 'pathologic' behaviour.[71] In addition, newly developed therapies should adhere more closely to the basic principles of meaningful motor learning, which requires proper assessment, training of meaningful skills graded to the level of difficulty, clear instructions, no overload, knowledge of results and performance, and varied repetition. Only if we are able to understand what is learned in motor control and how this knowledge is related to neural recovery, will we be able to determine the best way to present therapeutic exercises to the patient.

Hence, a better theoretical understanding of the underlying mechanisms of disordered movement coordination in terms of perception and action is needed for the development of more effective rehabilitation strategies. In order to allow for an adequate interpretation of the impact of the dynamics of fMRI findings on functional improvement of the upper paretic limb, the synergy dependent adaptations observed should be controlled kinematically over time.

REFERENCES

1. Aichner F, Adelwöhrer C, Haring HP. Rehabilitation approaches to stroke. J. Neural. Transm. 2002; 63 (suppl): 59–73.
2. Andrews R. Transhemispheric diaschisis. Stroke 1991; 22: 943–949.
3. Asanuma C. Mapping movements within a moving motor map. TINS. 1991; 14: 217–218.
4. Asberg KH. Orthostatic tolerance training of stroke patients in general medical wards: An experimental study. Scand. J. Rehabil. Med. 1989; 21: 179–185.
5. Atkinson PP, Atkinson JLD. Subject Review: Spinal shock. Mayo Clin. Proc. 1996; 71: 384–389.
6. Baron JC. Mapping the ischemic penumbra with PET: Implications for acute stroke treatment. 7th European Stroke Conference. Edinburgh. 1998.
7. Bhogal SK, Teasell R, Speechly M. Intensity of aphasia therapy: Impact on recovery. Stroke. 2003; 34: 987–993.

8. Bloedel JR, Ebner TJ, Wise SP. eds, The acquisition of motor behavior in vertebrates, Cambridge: MIT Press. 1996; pp. 440.
9. Boroojerdi B, Ziemann U, Chen R, Bütefisch CM, Cohen LG. Mechanisms underlying human motor system plasticity. Muscle and Nerve. 2001; 24: 602–613.
10. Brinkman J, Kuypers HG. Cerebral control of contralateral and ipsilateral arm hand and finger movements in split rhesus monkey. Brain. 1973; 96: 653–674.
11. Butler AJ, Wolf SL. Transcranial magnetic stimulation to assess cortical plasticity: A critical perspective for rehabilitation. J. Rehabil. Med. 2003; 41 (suppl): 20–26.
12. Calautti C, Leroy F, Guincestre JY, Baron JC. Dynamics of motor network overactivation after striatocapsular stroke: a longitudinal PET study using a fixed performance paradigm. Stroke. 2001; 32: 2534–2542.
13. Cao Y, D'Olhaberriague L, Vikingstad EM, Levin SR, Welch KMA. Pilot study of functional MRI to assess cerebral activation of motor function after post-stroke hemiparesis. Stroke. 1998; 29: 112–122.
14. Carey JR, Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey L, Rundquist P, Ugurbil K. Analyses of fMRI and finger tracking training in subjects with chronic stroke. Brain. 2002; 125: 773–778.
15. Carmichael ST, Tatsukawa K, Katsman D, Tsuyuguchi N, Kornblum HI. Evolution of Diaschisis in a Focal Stroke Model. Stroke. 2004; 35: 758–763.
16. Cirstea MC, Levin MF. Compensatory strategies for reaching in stroke. Brain. 2000; 123: 940–953.
17. Cozean CD, Pease WS, Hubbell SL. Biofeedback and functional electric stimulation in stroke rehabilitation. Arch. Phys. Med. Rehabil. 1988; 69: 401–405.
18. Cramer SC, Bastings EP. Mapping clinically relevant plasticity after stroke. Neuropharmacology. 2000; 39: 842–851.
19. Cramer SC, Mark A, Barquist K, Nhan H, Stegbauer KC, Price R, Bell K, Odderson R, Esselman P, Marravilla KR. Motor cortex activation is preserved in patients with chronic hemiplegic stroke. Annals of Neurology. 2002; 52: 607–616.
20. Cramer SC, Moore CI, Finklestein SP, Rosen BR. A pilot study of somatotopic mapping after cortical infarct. Stroke. 2000; 31: 668–671.
21. Cramer SC, Nelles G, Schaechter JD, Kaplan JD, Finklestein SP, Rosen BR. A fMRI study of three motor tasks in the evaluation of stroke recovery. Neurorehabilitation and Neural Repair. 2001; 15: 1–8.

22. Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, Kennedy DN, Finklestein SP, Rosen R. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke. 1997; 28: 2518–2527.
23. Cramer SC, Weisskoff RM, Schaechter JD, Nelles G, Foley M, Finklestein SP and Rosen RB. Motor cortex activation is related to force of squeezing. Human Brain Mapping. 2002; 16: 197–205.
24. Dijkhuizen RM, Moore CI, Glessner M, Rosen BR, Schaechter JD. Cortical surface-based functional MRI analysis of somatosensory and motor activation patterns in chronic stroke patients. Neurorehabilitation and Neural Repair. 2003; 17.
25. Dijkhuizen RM, Ren JM, Mandeville JB, Wu O, Ozdag FM, Moskowitz MA, Rosen BR, Finklestein SP. Functional magnetic resonance imaging of reorganisation in rat brain after stroke. Proceedings of National Academy of Sciences of the United States. 2001; 98: 12766–12771.
26. Dobkin BH. Editorial comment. Functional MRI: A potential physiological indicator for stroke rehabilitation interventions. Stroke. 2003; 34: 26–28.
27. Donoghue JP, Suner S, Sanes JN. Dynamic organization of primary motor cortex output to target muscles in adult rats. II. Rapid organization following motor nerve lesions. Exp. Brain Res. 1990; 79: 492–503.
28. Duncan PW, Min Lai S, Keighley J. Defining poststroke recovery: Implications for design and interpretation of drug trials. Neurol. Pharmacology. 2000; 39: 835–841.
29. Ernst E. A Review of stroke rehabilitation and physiotherapy. Stroke. 1990; 21: 1081–1085.
30. Feeny DM, Baron J. Diaschisis. Stroke. 1986; 17: 817–830.
31. Feydy A, Carlier R, Roby-Brami A, Bussel B, Cazalis F, Pierlot L, Burnod Y, Maier MA. Longitudinal study of motor recovery after stroke - Recruitment and focusing of brain activation. Stroke. 2002; 33: 1610–1617.
32. Foley NC, Teasell RW, Bhogal SK, Speechley MR. Stroke rehabilitation evidence-based review: methodology. Topics in Stroke Rehabilitation. 2003; 10: 1–8.
33. Friel KM, Nudo RJ. Recovery of motor functions after focal cortical injury in primates: compensatory movement patterns used during rehabilitative training. Somatosens. Mot. Res. 1998; 15: 173–189.
34. Furlan M, Marchal G, Viader GF, Derlon JM, and Baron JC. Spontaneous neurological recovery after stroke and the fate of ischemic penumbra. Ann. Neurol. 1996; 40: 216–226.

35. Ginsberg MD. Local metabolic response to cerebral ischemia. Cerebrovascular and Brain Metabolism Reviews. 1990; 2: 58–93.
36. Gresham GE. Stroke outcome research. Stroke. 1986; 17: 358–362.
37. Gresham GE, Duncan PW, Stason WB et al. Post-stroke rehabilitation, US Department of Health and Human services, Public Health service, Agency for Health Care Policy and Research. Rockville. 1995.
38. Hamrin II E. Early Activation in Stroke: Does it make a difference? Scand. J. Rehabil. Med. 1982; 14: 101–109.
39. Hayes SH, Carroll HM. Early intervention care in the acute stroke patient. Arch. Phys. Med. Rehabil. 1986; 67: 319–321.
40. Heald A, Bates D, Cartlidge NE, French JM, Miller S. Longitudinal study of central motor conduction time following stroke. 1. Natural history of central motor conduction. Brain. 1993; 116: 1355–1370.
41. Heald A, Bates D, Cartlidge NE, French JM, Miller S. Longitudinal study of central motor conduction time following stroke, 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. Brain. 1993; 116: 1371–1385.
42. Heddings AA, Friel KM, Plautz EJ, Barbay S, Nudo RJ. Factors contributing to motor impairment and recovery after stroke. Neurorehabil. and Neural Repair. 2000; 14: 301–310.
43. Heller A, Wade DT, Wood VA, Sunderland A, Hewer RLL. Arm function after stroke: Measurement and recovery over the first three months. J. Neurol. Neurosurg. Psychiatry. 1987; 50: 714–719.
44. Hendricks HT, Limbeek van J, Geurts AC, Zwarts MJ. Motor recovery after stroke: a systematic review of the literature. Arch. Phys. Med. Rehabil. 2002; 83: 1629–1637.
45. Hennig J, Speck O, Koch MA, Weiller C. Functional magnetic resonance imaging: a review of methodological aspects and clinical applications. J. Magn. Reson. Imaging. 2003; 18: 1–15.
46. Hesse S., Bertelt C., Jahnke MT, Schaffrin A, Baake P, Malezic M, Mauritz KH. Restoration of gait in nonambulatory hemiparetic patients by treadmill training with partial body-weight support. Arch. Phys. Med. Rehabil. 1994; 75: 1087–1093.
47. Hesse S, Bertelt C, Jahnke MT, Schaffrin A, Baake P, Malezic M, Mauritz KH. Treadmill training with partial body weight support compared with physiotherapy in nonambulatory hemiparetic patients. Stroke. 1995; 26: 976–981.

48. Rasmussen KH, Skinhoj E. Transneural depression of the cerebral hemispheric depression in man. Acta Neurol. Scand. 164; 40: 41–46.
49. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Stroke unit treatment, 10-year follow-up. Stroke. 1999; 30: 1524–1527.
50. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Treatment a combined acute and rehabilitation stroke unit: which aspects are the most important? Stroke. 1999; 30: 917–923.
51. Berg HJ, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitation therapy. Brain. 2002; 125: 2731–2742.
52. Berg HJ, Rushworth MFS, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of the ipsilateral motor cortex in hand movement after stroke. Proceedings of National Academy of Sciences of the United States. 2002; 99: 14518–14523.
53. Kalil K. Regeneration of pyramidal tract axons, Adv in Neurology, in: Functional recovery in neurological disease. (Vol. 47). S.G. Waxman. ed. Raven Press, New York. 1988; pp. 67–85.
54. Kalra L. The influence of stroke unit rehabilitation on functional recovery from stroke. Stroke. 1994; 25: 821–825.
55. Kato H, Kogure K. Biochemic and molecular characteristics of the brain with developing cerebral infarctions. Cellular and Molecular Neurobiology. 1999; 19: 93–108.
56. Kato H, Izumiyama M, Koizumi H, Takahashi A, Itoyama Y. Near-infrared spectroscopic topography as a tool to monitor motor reorganisation after hemiparetic stroke. Stroke. 2002; 33: 2032–2036.
57. Kaufmann AM, Firlik AD, Fukui MB, Wechsler LR, Jungries CA, Yonas H. Ischemic core and penumbra in human stroke. Stroke. 1999; 30: 93–99.
58. Kleim JA, Lussing E, Schwartz ER, Comery TA, Greenough WT. Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. J. Neuroscience. 1996; 16: 4529–4535.
59. Kwakkel G, Kollen BJ, Wagenaar RC. Long term effects of intensity of arm and leg training in stroke patients: A randomized trial. J. Neurol. Neurosurg. Psychiat. 2002; 72: 473–479.
60. Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation: A critical review of the literature. Physiotherapy. 1999; 85: 377–391.

61. Kwakkel G, Kollen BJ, Grond van der J, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb. The impact of severity of paresis and time since onset in acute stroke. Stroke. 2003; 34: 2181–2186.
62. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet. 1999; 354: 191–196.
63. Kwakkel G, Wagenaar RC, Koelman TW, Lankhorst GJ, Koetsier JC. Effects of intensity of stroke rehabilitation. A research synthesis. Stroke. 1997; 28: 1550–1556.
64. Kwakkel G, Wagenaar RC. Effect of duration of upper- and lower-extremity rehabilitation sessions and walking speed on recovery of interlimb coordination in hemiplegic gait. Phys. Ther. 2002; 82: 432–448.
65. Langhorne P, Pollock A. What are the components of effective stroke unit care? Age Ageing. 2002; 31: 365–371.
66. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? Lancet. 1993; 342: 395–398.
67. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? British Medical Journal. 1094; 309: 1273–1277.
68. Langhorne P, Duncan PW. Does the organization of postacute stroke care really matter? Stroke 2001; 32: 268–274.
69. Langhorne P, Wagenaar RC, Partridge C. Physiotherapy after stroke: More is better? Physiotherapy Res. Int. 1996; 1: 75–88.
70. Lassen NA, Fieschi C, Lenzi GL. Ischemic penumbra and neuronal death: Comments on the therapeutic window in acute stroke with particular reference to thrombolytic therapy. Cerebrovasc. Dis. 1991; 1(suppl): 32–35.
71. Latash ML, Anson JG. What are "normal" movements in atypical populations? Behavioral and Brain Sciences. 1996; 19: 55–106.
72. Lee RG, Donkelaar van P. Mechanisms underlying functional recovery following stroke. Can. J. Neurol Sci. 1995; 22: 257–263.
73. Lenzi GL, Frackowiak SJ, Jones T. Cerebral oxygen metabolism and blood flow in human cerebral infarction. J. Cerebral Blood Flow Metabolism. 1982; 2: 321–335.
74. Levy CE, Nichols DS, Schmalbrock PM, Keller P, Chakeres DW. Functional MRI evidence of cortical reorganisation in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. Am. J. Phys. Med. Rehabil. 2001; 80: 4–12.

75. Liepert J, Hamzei F, Weiller C. Motor cortex disinhibition of the unaffected hemisphere after acute stroke. Muscle & Nerve. 2000; 23: 1761–1763.
76. Liepert J, Bauder H, Miltner WHR, Taub E, Weiller C. Treatment induced cortical reorganisation after stroke in humans. Stroke. 2000; 31: 1210–1216.
77. Marchal G, Benali K, Iglesias S. Voxel-based mapping of irreversible ischemic damage with PET in acute stroke. Brain. 1999; 123: 2387–2400.
78. Marchall RS, Perera GM, Lazar RM, Krakauer JW, Constantine RC, DeLaPaz RL. Evolution of cortical activation during recovery from corticospinal tract infarction. Stroke. 2000; 31: 656–661.
79. Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. Topographical reorganization of somatosensory cortical areas 3b and 1 in adult monkeys followed restricted deafferentiation. Neuroscience. 1983; 8: 33–55.
80. Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. J. Comparative Neurol. 1984; 224: 591–605.
81. Nelles G, Spiekerman G, Jueptner M, Leonardt G, Müller SM, Gehard HS, Diener HC. Evolution of functional reorganization in hemiplegic stroke: A serial positron emission tomographic activation study. Ann. Neurol. 1999; 46: 901–909.
82. Newton J, Sunderland A, Butherworth SE, Peters AM, Peck KK, Gowland PA. A pilot study of event related functional magnetic resonance imaging of monitored wrist movements in patients with partial recovery. Stroke. 2002; 33: 288–2887.
83. Nudo RJ, Plautz EJ, Frost SB. The role of adaptive plasticity in recovery of function after damage to motor cortex. Muscle Nerve. 2001; 24: 1000–1019.
84. Nudo RJ. Adaptive plasticity in motor cortex: Implications for rehabilitation after brain injury. J. Rehabil. Med. 2003; 41: 7–10.
85. Ottenbacher KJ, Jannell S. The results of clinical trials in stroke rehabilitation research. Arch. Neurol. 1993; 50: 37–44.
86. Pantano P, Formisano R, Ricci M, Piero VD, Sabatini U, Pofi BD, Rossi R, Bozzao L, Lenzi GL. Motor recovery after stroke. Morphological and functional brain alterations. Brain. 1996; 119: 1849–1857.
87. Phan TG, Wright PM, Markus R, Howells DW, Davis SM, Donnan GA. Salvage the ischaemic penumbra: More than just reperfusion? Clin. and Exp. Pharmacology and Physiology. 2002; 29: 1–10.

88. Pineiro RS, Pendlebury S, Berg HJ, Matthews PM. Functional MRI detects posterior shifts in primary sensorimotor cortex activation after stroke. Stroke. 2001; 32: 1134–1139.
89. Pineiro RS, Pendlebury S, Berg HJ, Matthews PM. Altered hemodynamic responses in patients after subcortical stroke measured by functional MRI. Stroke. 2002; 33: 103–109.
90. Platz T, Kim IH, Engel U, Kieselbach A, Mauritz KH. Brain activation pattern as assessed with multi-modal EEG analysis predicts motor recovery among stroke patients with mild arm paresis who receive the Arm Ability Training. Restor. Neurol. Neurosci. 2002; 20: 21–35.
91. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. Stroke. 1999; 30: 1384–1389.
92. Rema V, Armstrong M, James M, Ebner FF. Experience-dependent plasticity of adult rat S1 cortex requires local NMDA receptor activation. J. Neruroscі. 1998; 18: 10196–10206.
93. Roby RR. A meta-analysis of clinical outcomes in the treatment of aphasia. J. Speech Hearing Res. 1998; 41: 172–187.
94. Rønning OM, Guldvog B. Outcome of subacute stroke rehabilitation: A randomized controlled trial. Stroke. 1998; 29: 779–784.
95. Rossini PM, Caltagirone C, Scanderbeg AC, Cicinelli P, Gratta CD, Demartin M, Pizzella V, Traversa R, Romani GL. Hand motor cortical area reorganisation in stroke: a study with fMRI, MEG and TCS maps. NeuroReport. 1998; 9: 2141–2146.
96. Roth EJ. The elderly stroke patient: Principles and practices of rehabilitation management. Topics in Geriatric Rehabilitation. 1988; 3: 27–61.
97. Rothi LJ, Horner J. Restitution and substitution: Two theories of recovery with application to neurobehavioral treatment. J. Clin. Neurophysiology. 1982; 51: 73–81.
98. Schaechter JD, Kraft E, Hilliard TS, Dijkhuizen RM, Benner T, Finklestein SP, Rosen BR, Cramer SC. Motor recovery and cortical reorganisation after constraint induced movement therapy in stroke patients. Neurorehabilitation and Neural Repair. 2002; 16: 326–338.
99. Seil FJ. Recovery and repair issues after stroke from the scientific perspective. Current Opinion in Neurology. 1997; 10: 49–51.
100. Seitz RJ, Azari NP, Kmorr U, Binkofsky F. The role of diaschisis in stroke recovery. Stroke. 1999; 30: 1844–1850.

101. Shelton F, Reding MJ. Effect of lesion location on upper limb motor recovery after stroke. Stroke. 2001; 32: 107–112.
102. Cook AS, Anson D, Haller S. Postural sway biofeedback: Its effect on reestablishing stance stability in hemiplegic patients. Arch. Phys. Med. Rehabil. 188; 69: 395–400.
103. Sinha S, Warburton EA. The evolution of stroke units – toward a more intensive approach? Q. J. Med. 2000; 93: 633–638.
104. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after Stroke. J. Neurol. Neurosurg. Psychiat. 1983; 46: 5–8.
105. Small SL, Hlustik P, Noll DC, Genovese C, Solodkin A. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. Brain. 2002; 125: 1544–1557.
106. Smith ME, Garraway WM, Smith DL, Akthar AJ. Therapy impact on functional outcome in a controlled trial of stroke rehabilitation. Archives of Physical Medicine and Rehabilitation. 1982; 63: 21–24.
107. Sonde L, Nordstrom M, Nilsson CG, Lokk J, Viitanen M. A double-blind placebo-controlled study of the effects of amphetamine and physiotherapy after stroke. Cerebrovasc. Dis. 2001; 12: 253–257.
108. Staines WR, McIlroy WE, Graham SJ, Black SE. Bilateral movement enhances ipsilesional cortical activity in acute stroke: a pilot functional MRI study. Neurology. 2001; 56: 401–404.
109. Steenbergen B. The planning and coordination of prehension movements in spastic hemiparesis. Quickprint, Nijmegen. 2000.
110. Stroemer RP, Kent TA, Hulsebosch CE. Neocortical neural sprouting, synaptogenesis, and behavioural recovery after neocortical infarcts in rats. Stroke. 1995; 26: 2135–2144.
111. Stroke Trialists' Collaboration. Collaborative systematic review of randomised trials of organised inpatient (stroke unit) care after stroke. British Medical Journal. 1997; 314: 1151–1159.
112. Sunderland A, Tinson DJ, Bradley L, Hewer RL. Arm function after stroke: An evaluation of grip strength as a measure of recovery and prognostic indicator. J. Neurol. Neurosurg. Psychiat. 1989; 52: 1267–1272.
113. Takasawa M, Watanabe M, Yamamoto S, Hoshi T, Sasaki T. Prognostic Value of subacute crossed-cerebellar diaschisis: Single-photon emission CT study in patients with middle cerebral artery territory Infarct. Am. J. Neuroradiol. 2002; 23: 189–193.

114. Taub E, Miller NE, Novack TA, Cook EW, Fleming WC, Nepomuceno CS, Conell JS, Crago JE. Technique to improve chronic motor deficit after stroke. Arch. Phys. Med. Rehabil. 1993; 74: 347–354.
115. Teasell RW, Jutai JW, Bhogal SK, Foley NC. Research gaps in stroke rehabilitation. Topics in Stroke Rehabilitation. 2003; 10: 59–71.
116. Twitchell TE. The restoration of motor function following hemiplegia in man. Brain. 1951; 74: 443–480.
117. Monakow CV. Die lokalisation im grobhirn und der abbau der function durch kortikale herde, Wiesbaden: Bergmann. 1914.
118. Wade DT. Research into the black box of rehabilitation: The risk of a type III error. Clin. Rehabil. 2001; 15: 1–4.
119. Wagenaar RC, Meijer OG. Effects of stroke rehabilitation (1). J. Rehabil. Sci. 1991; 4: 61–73.
120. Wagenaar RC, Meijer OG. Effects of stroke rehabilitation (2), J. Rehabil. Sci. 1991; 4: 97–109.
121. Wagenaar RC. Functional recovery after stroke, Amsterdam: VU University Press. 1990.
122. Ward NS, Brown MM, Thomposon AJ, Frackowiak RSJ. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain. 2003; 126 (epub update, august).
123. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of outcome after stroke: A crossectional fMRI study. Brain. 2003; 126: 1430–1441.
124. Webb DJ, Fayad PB, Wilbur C, Thomas A, Brass LM. Effects of a specialized team on stroke care. Stroke. 1995; 26: 1353–1357.
125. Webster JS, Jones S, Blanton P, Gross R, Beissel GF, Wofford J. Visual scanning training with stroke patients. Behavioral Therapy. 1984; 15: 129–143.
126. Weiller C, Chollet F, Friston KJ, Wise RJS, Frackowiak RSJ. Functional reorganization of brain in recovery from striatocapsular infarction in man. Ann. Neurol. 1992; 31: 463–472.
127. Weiller C, Ramsey SC, Wise RJS, Friston KJ, Frackowiak RSJ. Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. Ann. Neurol. 1991; 29: 63–71.
128. Winstein CJ, Gardner ER, McNeal DR, Barto PS, Nicholson DE. Standing balance training: effect on balance and locomotion in hemiparetic adults. Arch. Phys. Med. Rehabil. 1989; 70: 755–762.

129. Dauphinee SW, Kwakkel G. The impact of rehabilitation on stroke outcome: What's the evidence? In: Stroke rehabilitation, M. Barnes, ed., Bogousslavsky Dobkin, in press.
130. Zemke AC, Heagerty PJ, Lee C, Cramer SC. Motor cortex organization after stroke is related to side of stroke and level of recovery. Stroke. 2003; 34: e23–e28.

CHAPTER 10

General discussion

INTRODUCTION

Stroke is a complex disorder and complex is recovery from it. With the institutionalization of stroke services across health care facilities, a reduction in mortality rates, length of inpatient stay and improved independence in activities of daily living has been achieved. However, stroke remains the leading cause of long-term disability. Moreover, it is a condition for which there is no universally accepted rehabilitation approach (chapter 2). Much remains to be learned from stroke recovery and the effects of stroke rehabilitation.

This thesis describes the long term recovery of hemiplegic gait in severely affected stroke patients. Based on the application of a repeated measurement research design, data were obtained within the first post-stroke year period. This information subsequently enabled the identification of time-related changes and was used to address the following main questions:
Are intensive stroke rehabilitation programmes, implemented within the early and subacute post-stroke phases, worthwhile in terms of long term functional gains and can this long term recovery be estimated early after stroke onset for better individualized reliable therapeutic goal setting and discharge planning?
For this purpose, early and late recovery patterns were studied as functional recovery after stroke tends to be non-linear and time-dependent. Subsequently, this information was used in the interpretation of some of the mechanisms involved in the long term recovery of hemiplegic gait and the impact of intensity of therapeutic interventions on this recovery.
The main findings of the studies presented in the first part of this thesis indicate predictive relationships between early determinants and late outcome and the relevance of measuring frequently and longitudinally in order to take into consideration the non-linear time-dependent relationship of covariates with recovery of gait after stroke. In the second part it is demonstrated that the long term effects of intensity of stroke rehabilitation, implemented during the initial 20 post-stroke weeks, are maintained for up to one year.

PREDICTING RECOVERY OF GAIT AFTER STROKE

Although adherence to major methodological principles in prognostic research is a prerequisite for achieving internal and statistical validity, heterogeneity of the stroke population remains a major threat to the external validity of prediction models when these models are based on insufficient large patient samples (chapter 2).[1,2,3,4] Generating a large patient sample in a clinical setting is often difficult to materialize. Therefore, stratification of patients based on demographic and diagnostic data has been recommended in order to increase precision of prediction models.[1,2,4,5,6] The aim of applying prediction models in more specific subpopulations of stroke patients is to strike a balance between precision and generalizability. In chapter 4 we described the development of a longitudinal prediction model based on a relative homogeneous stroke population for the identification of significant variables. All 101 subjects suffered a severe middle cerebral artery stroke and none were ambulatory at the first post-stroke week. Selection of variables was based on consistency in predicting outcome throughout the entire initial 10 week period after stroke. In the final multivariate logistic regression models age and Barthel Index (BI) proved to be the most robust variables in the prediction of independent walking outcome at six months (Functional Ambulation Categories: FAC ≥4). Low age and high BI were associated with a high probability of independent hemiplegic gait at 6 months. However, high sensitivity coincided with moderate specificity of the prediction models. As a consequence prediction within the acute and subacute phases (initial 10 weeks) of stroke patients who will fail to regain independent gait at 6 months was less reliable. This finding suggests that when in doubt the clinician should consider age and BI when planning discharge, rehabilitation or home care services.

The probability of regaining independent gait at 6 months for an individual with a BI of 5 points in week 4 diminishes with about 10 percent each added 5 years of age between 55 (81%) and 70 (46%), but for a individual of 65 years of age the difference in probabilities between 5 and 10 BI points (59% versus 92 %) is much more pronounced than between 10 and 15 BI points (92% versus 99%).

These findings suggest a linear relationship for age and a non-linear relationship for BI with independent gait. Table 1 provides the formulas generated by the logistic prediction model for the calculation of probabilities of achieving independent gait at 6 months.

Table 1. Formulas for probabilities of regaining independent gait at 6 months post-stroke.

Week	Diagnostic model
1	1 / {1 + EXP[-(11.508 – 0.146 * age)]}
2	1 / {1 + EXP[-(6.694 - 0.126 * age + 0.311 * BI)]}
3	1 / {1 + EXP[-(5.306 - 0.105 * age + 0.050 * TCT)]}
4	1 / {1 + EXP[-(5.344 - 0.107 * age + 0.399 * BI)]}
5	1 / {1 + EXP[-(4.781 - 0.101 * age + 0.379 * BI)]}
6	1 / {1 + EXP[-(6.572 - 0.128 * age + 0.361 * BI)]}
7	1 / {1 + EXP[-(7.357 – 0.150 * age + 0.423 * BI)]}
8	1 / {1 + EXP[-(3.938 – 0.121 * age + 0.521 * BI)]}
9	1 / {1 + EXP[-(3.461 – 0.106 * age + 0.451 * BI)]}
10	1 / {1 + EXP[-(3.166 – 0.117 * age + 0.503 * BI)]}

Exp, Exponential function (anti-logarithm); BI, Barthel Index; TCT, Trunk Control Test

The results of this study also indicate the complexity of recovery because even in these robust variables observing false positive cases is not uncommon. Moreover, not all true non-ambulatory patients will be initially classified as non-walkers. As a consequence some patients may qualify for post-acute rehabilitation services and be subjected to gait training without showing a potential for mastering functional independence in gait. This may lead to a wrongful investment of resources, time and effort from health care professionals and raised expectations on the part of the patient. Diminished specificity of the prediction model is responsible for its failure to predict all true non-ambulatory patients.

Non-linearity and time-dependency are characteristic elements of stroke recovery (chapter 2). However, whether there are any constant elements to be identified in this relationship in stroke recovery is a question addressed in chapter 3.
In this chapter the nature of the relationship between safe comfortable and maximal walking speed was explored in 81 stroke patients. The results of this study showed that in marked hemiplegic stroke patients (FAC ≥3) maximum

walking speed can be reliably estimated by comfortable walking speed time measurement expressed in meters per second (m/s). It was found that maximum speed equals 1.32 times comfortable speed. This relation remained constant after adding co-variables to the regression models in an attempt to increase the precision, such as the patients' age, balance, hemiplegic arm and leg muscle strength and type of therapeutic intervention. It was concluded that the relationship between safe comfortable and maximum walking speeds is fixed in post-stroke time. This fixed relationship suggests that these two parameters are defined at a biomechanical level in stroke irrespectively of gender, age, time following onset or its severity. More research is needed to determine the nature of this biomechanical fixed relationship between comfortable and maximum walking speed. Only longitudinal study designs can address such a relationship in stroke recovery. These designs may assist in elucidating the biomechanical principles that are likely to govern this relationship in the stroke population as to date the exact nature of this relationship is not yet fully understood.

Training at higher walking speeds is likely to better prepare stroke patients for meeting the demands imposed by independent community living. However, more research is needed to determine if maximum walking speed training needs to be considered a therapeutic adjunct that should be incorporated in stroke rehabilitation programmes.

To underscore the complexity of stroke recovery and its measurement, we explored the longitudinal relationship between comfortable walking speed and the classification of physical independent gait (FAC ≥ 3) over time in 73 stroke patients in chapter 5. First, it was shown that comfortable walking speed is sensitive enough to detect clinically important changes and therefore is suitable for demonstrating pretest-posttest time-related post-stroke changes in independent gait in our population. Based on random coefficient analysis over the entire study period, significant time-dependent effects were demonstrated between walking speed and FAC scores for physically independent gait, ie, this relationship is subject to time related longitudinal changes. In addition, the pretest-posttest walking speed and FAC observations showed an emerging pattern of changing walking speeds coupled with high correlated pretest-posttest

FAC appraisals. There are indications that, in this relationship, repeated FAC appraisals are not only based on steady walking speeds, but that the walking speeds related to a specific FAC appraisal also change and, over time, may shift gradually from higher to lower speeds. This finding suggests that a critical appraisal of the outcome of repeated measurements remains important as unexpected phenomena (such as shift) may interact with clinimetric sound instruments and as a consequence may affect clinical decision making.

Several classifications based on aetiology, subtype, topography of stroke on CT or MRI scan and clinical neurological manifestation have been suggested by epidemiologists for stratification of acute stroke patients.[7] However, the usefulness of many of these classifications for epidemiological and clinical studies is limited due to a lack of reliable differentiation between classes[7] as well as a lack of predictive validity of the classification of interest with respect to outcome.[2] It has been hypothesised that some homogeneity can be created by composing subgroups with an identical underlying process, enabling treatments to be focused on particular subgroups of stroke patients.[8] A number of authors have argued that certain subgroups of the stroke population may benefit more than other subgroups from specific rehabilitation services. In order to achieve the most efficient use of such services, it is important to identify predictors that discriminate between stroke patients with good and poor prognosis.[9,10,5] We were able to demonstrate such a subgroup but could not identify the specific defining characteristics of these patients (chapter 8). This chapter describes the outcome of a randomized controlled trial conducted to study the long term effects of intensity of stroke rehabilitation in 101 patients. The impact of intensity on three randomized intervention groups was studied. Basic rehabilitation programmes were supplemented with either extra upper or lower extremity training or air splint immobilization. Outcome was based on several ADL and quality of life measures. It was found that the long term effects of intensity of stroke rehabilitation during the initial 20 post-stroke weeks were maintained for up to one year. However, a significant number of patients with incomplete recovery showed improvements or deterioration of walking ability and ADL beyond the error threshold between 6 and 12 months post-stroke. The identification of this subgroup of stroke patients is the first step towards improving stroke care as it then becomes possible to target specific stroke populations in an attempt to optimize individual stroke rehabilitation.

The classification based on the BI has been proposed for its reliability and high predictive validity with respect to outcome of disability.[10,11,12] Our study described in chapter 4 confirmed this finding but also found age of the patient to be predictive of outcome of walking at 6 months. Within our stroke population, each added year of age reduced the probability of regaining independent gait 0.9 times, while at the same time each higher BI point improved chances 1.4 to 1.7 times depending on the week of prediction. However, more research is needed to elucidate the negative association observed between age and independent gait. Do older individuals suffer more severe strokes or are perhaps premorbid factors responsible for this declining probability?
Besides heterogeneity of the stroke population, differences within and between studies in post-stroke timing of measurements taken for prediction decrease external validity of existing prediction models.[1,2,4] The development of new effective therapeutic strategies relies on a better understanding of the mechanisms underlying recovery of function. Addressing the question of what needs to be learned precedes the question of how it should be learned.[13] This may partially explain the failure to demonstrate overloading effects on walking speed as discussed in chapter 7. This study describes a pilot study conducted to investigate the effects of overloading of the lower extremity on walking speed in three chronic stroke patients. It was hypothesized that overloading the hemiparetic lower extremity would generate increased motor output resulting in carry-over effects. In some sports these effects are commonly used in order to improve performance. Overloading was based on the randomized application of 2 and 6 lbs weight cuffs to the distal paretic lower extremity. A single subject withdrawal design study showed a gradual improvement in comfortable walking speed between subsequent days but failed to demonstrate any immediate favourable effects on comfortable walking speed as a direct result of limb

overloading. This finding suggests that this training concept requires further scrutiny because of the improvements observed over time. It also indicates the usefulness of small scale research projects to pilot a research question. Therefore, to test a research question it is certainly feasible to use a single subject design as a preliminary study before deciding on the implementation of a randomized controlled trial.

METHODOLOGICAL ASPECTS

Traditionally, cross-sectional stroke research is conducted. Pretest-posttest measurements are performed in one or two groups and subsequently analysed. When attempts are made to relate the outcome of such a research project to the results of similar projects, it is not uncommon to find that different time points of measurement as well as dissimilar measurement instruments are used. The variability in timing of the assessment of final outcome has made comparisons between prognostic studies difficult.[1] This presents a problem in systematic reviews as the lack of uniformity limits mutual comparison let alone the pooling of results for meta-analysis. In stroke research the non-linear functional recovery pattern presents challenges to overcome and calls for an inception cohort with repeated measurements taken at fixed times post-stroke. To date in stroke research, there are only few longitudinal studies published that used repeated measurements over time.

Wagenaar observed a sigmoidal (S-shaped) form for individual recovery patterns.[14] As most improvement tends to occur early following stroke, weekly measurements are required within this period. We obtained weekly measurements during the initial 10 week post-stroke onset period followed by biweekly measurements until the 20th week. Thereafter, follow-up measurements were done at 26, 38 and 52 weeks. Based on the outcome of these measurements, this thesis provides a better understanding of the necessity to measure frequently, longitudinally and at standardized times. Tilling et al advocate the use of multilevel growth curve models with covariate effects based on repeated measurements to describe patterns of stroke recovery.[15]

In our research project reliable, valid and responsive measurement instruments were used for all functional assessments that were done by one observer who was blinded for treatment assignment. A major advantage of frequently repeated measurements over time is that the generated information represents reality far better than the information gathered from one or two measurements (chapter 2). This in turn allows for a more valid interpretation of reality as it enables observing changes in actual recovery processes that take place over time. Longitudinal modelling of change scores may provide a better understanding of the quasi-causal relationship between body functions and structures, activities and participation.[16] In chapter 6 we studied the longitudinal relationship of functional change in walking ability and change in time-dependent covariates and developed a multivariate regression model to predict longitudinal change of walking ability. In regular multi-level hierarchical regression modelling the regression coefficients presented, collectively reflect the cross-sectional (ie, between subjects-variation) as well as the longitudinal relationship (ie, within-subject variation) between determinant(s) and outcome. This constitutes a limitation when the absolute differences between subjects exceed the changes over time within subjects. As a result the longitudinal within-subject relationships will be more or less overruled by the cross-sectional relationships.[17] This is likely to occur when time periods between repeated measurements are relatively short and the within-subject correlation high. Because of this limitation, we used a model in which the cross-sectional component is more or less 'removed' from the analysis by modelling only change scores.[17] Based on our analysis, we found that for achieving improvement in walking ability, improvement in standing balance was more important than improvement in leg synergism or strength. This suggests that in order to meet the objective of improving gait stroke rehabilitation should include an intensive balance training programme although more research is needed to establish a causal relationship between balance training and improvement in gait.

In addition, reduction in visuo-spatial inattention was predictive of improvement in gait. In other words, unabated neglect may hamper efforts to improve gait after stroke. Our findings also indicate that time itself is an independent covariate which is negatively associated with change on FAC. This latter observation suggests that most pronounced improvements occur early after stroke onset and that critical time windows may play a role in functional recovery.

The statistical approach of modelling change scores holds much promise for the future as its use facilitates the unravelling of the time-dependent components of functional recovery after stroke. This in turn may help to elucidate the underlying mechanisms responsible for the non-linear patterns of recovery observed after stroke.

Longitudinal research based on clinimetric data and data obtained from neurophysiological techniques, such as Transcranial Magnetic Stimulation (TMS), as well as neuroimaging, such as functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET), may increase our knowledge of neural plasticity by linking cerebral adaptive changes and concomitant observed recovery profiles of impairments and activities.[12]

However, as to be expected longitudinal designs also carry some disadvantages. Because more patients are needed who are also closely followed over time this clinimetric approach is more costly and laborious than traditional cross-sectional research and therefore may be difficult to implement without financial support. Because the within subject variability between longitudinal measurements (expressed as the within subject correlation coefficient ρ) is added to the numerator of the fraction to calculate the minimal sample size for a study using a repeated measurement design, such a design necessitates a larger patient sample. Therefore, within the same number of repeated measurements and differences, the lower the within variability (higher ρ) the more subjects are required. However, increasing the number of repeated measurements coincides with a decreasing sample size.[17]

CONCLUDING REMARKS WITH A FOCUS ON FUTURE RESEARCH

In most regression models developed to date, the clinical predictors included are assumed to be fixed, implying that they do not change over time as a result of recovery. Our findings indicate that clinical determinants show considerable improvement in the early stages after stroke onset. More research is needed for the development of prognostic models based on the within-subject variability of covariates and uniform timing of prediction and assessment of final outcome. In our studies of the relationship between comfortable and maximum walking speeds (chapter 3) and time dependency of walking classification (chapter 5) we applied a regression model that analyzed the within and between subject variability simultaneously. The former study showed a predictable stable relationship between both speeds over time after stroke. The latter study clearly demonstrated an association between walking classification and walking speed measurements over time. This association was also subject to a time related decline. Many time-dependent variables are yet to be determined, but from the results of our study conducted to predict improvement in gait over time it becomes evident that time itself is a strong determinant for functional recovery after stroke (chapter 6). However, future research should focus on the identification of other time-dependent determinants. This information can than be used to determine critical time windows for specific therapeutic interventions but may also assist in identifying hierarchy in recovery patterns.[18] The use of mixed modeling statistical techniques allows for the analysis of cross-sectional and longitudinal treatment and time effects simultaneously while correcting for the correlated observations within subjects over time and allowing for regression coefficients to differ between subjects. As time constitutes an independent covariate in such a model, these statistical methods enable longitudinal analysis of unequally spaced time points of measurement. Moreover, in random coefficient analysis missing data are presumed to be missing at random.[17] Few attempts are made to study emerging longitudinal patterns in stroke presentation. Our finding of the presence of a constant between comfortable and maximal walking speeds in stroke patients is an example of such a pattern (chapter 3). The issue of elucidating possible longitudinal associations between patterns observed in stroke recovery requires more attention. Which rationale can explain an observed pattern? To date no clear answers are formulated. Knowledge is lacking of any tools that can be used to establish a plausible rationale. Energetic and biomechanical related mechanisms may be involved in this fixed pattern in stroke patients and deserve further scrutiny in future research.

The impact of therapy induced changes on stroke recovery was studied in our randomized controlled trial on the long term effects of intensity of training (chapter 8). The results of this study suggest that intensity of stroke rehabilitation may accelerate recovery. While the effects are maintained until one year post-stroke, intensity of stroke rehabilitation is not likely to produce additional activities, ie, better long term walking ability and ADL. At first sight these findings may appear insignificant. However, they are not. Faster recovery means a lower probability of complications, earlier discharge to home and fewer costs to society. It should be noted that a lack of statistical power may have been responsible for the inability to demonstrate any long term additional benefits of increased intensity of stroke rehabilitation. Therefore, multi-center trials with adequate power are needed to further investigate possible additional benefits of stroke rehabilitation. In the present study a subgroup of patients was found with incomplete functional recovery at 6 months that showed large subsequent changes (including both improvements and deterioration) in body functions and activities. This observation indicates that there is potentially a subgroup of patients in who increased therapy could be targeted at a later stage. However, identifying the characteristics of these patients, who are exceptions to this general rule and would benefit from later intervention to optimize their recovery, is a challenge that should be addressed in future research.
The non-linear pattern as a function of time is not well understood. Chapter 9 discusses the mechanisms that are presumably involved in the pattern of functional recovery after stroke. These include recovery of penumbral tissues, neural plasticity, resolution of diaschisis and behavioural strategies. Based on

information from prediction models that are adjusted for the effects of time after stroke onset, it can be derived that outcome is largely defined within the first weeks post-stroke. However, functional improvement has been found to extend beyond six months post-stroke. Kinematic studies show that functional improvement is more than recovery from impaired body functions alone. In other words, there are strong indications that motor recovery after stroke occurs to a large extent through behavioural compensation, rather than via processes of 'true recovery' alone. For instance, it was shown that recovery to a large extent is due to the implementation of strategies that allow for the compensation of existing impairments in the lower hemiparetic extremity.[19] That study demonstrated that increasing walking speed resulted in relatively larger increments in arm and leg swing on the non-paretic side than on the paretic side. In other words, the contribution to the increased walking speed by alternating arm and leg swings was found to be larger on the non-hemiplegic side than on the hemiplegic side of the body. One may conclude that functional recovery is not only a matter of restoration or restitution but also involves compensation by using alternative strategies to achieve the intended goal. In fact, behavioural compensation strategies are considered to be potential confounders in our understanding of 'neural repair' and related cerebral recovery after stroke.[20] Normal motor behaviour of healthy subjects should not serve as a measure of reference for understanding the adaptive motor behaviour of hemiparetic stroke patients.[21] Although several neurological treatment approaches, such as Neurodevelopment Treatment (NDT), suggest that compensatory movements may potentially inhibit a return to normal functioning and therefore their use should be discouraged evidence for this assumption is lacking.[22,23] This may explain why more functionally oriented compensatory therapies, such as Motor Relearning Programme[24], achieve their functional goals sooner than remedial therapies that do not allow for behavioural compensation (chapter 2). This finding is supported by a recent study of Bode et al who showed that, after controlling for the stroke severity, greater than expected gains in self-care were predicted by longer lengths of stay and more intensive function-focused occupational therapy. However, in this study predictors of residual change in mobility differed by gender: greater than expected gains in mobility for men were predicted by longer lengths of stay and more intense function-focused physical therapy whereas, for women, they were predicted by stroke severity alone.[25]

Future studies may explore the relationship between behavioural adaptations and improved skills after stroke, ie, addressing the issue of which changes in motor control coincide with functional improvements. This knowledge may contribute to determining the best way in which to subject stroke patients to therapeutic exercises.

REFERENCES

1. Jongbloed L. Prediction of function after stroke: a critical review. Stroke. 1986; 17: 765-776.
2. Gresham GE. Stroke outcome research. Stroke 1986; 17: 358-362.
3. Gladman JRF, Harwood DMJ, Barer DH. Predicting the outcome of acute stroke: prospective evaluation of five multivariate models and comparison with single methods. Journal of Neurology, Neurosurgery and Psychiatry. 1992; 55: 347-351.
4. Vanclay F. Functional outcome measures in stroke rehabilitation. Stroke. 1991; 22: 105-108.
5. Hier DB, Edelstein G. Deriving clinical prediction rules from stroke outcome research. Stroke. 1991; 22: 1431-36.
6. Dombovy ML, Basford JR, Whisnant JP, Bergstrahl EJ. Rehabilitation for stroke: A review. Stroke. 1986; 17: 363-9.
7. Castillo V, Bogousslavsly J. Early classification of stroke. Cerebrovascular Disease. 1997; 7 (suppl 3): 5-11.
8. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991; 337: 1521-26.
9. Gresham GE, Duncan PW, Statson WB. ‘Priorities for future research’. Clinical practice guidelines number 16, US department of health and human services, Agency for health care policy and research, Rockwell, Maryland, AHCPR publication. 1995; no. 95-0662.

10. Wade DT, Langton-Hewer R. Rehabilitation after stroke. In: Vinken PJ, Bruyn GW, Klawans JL, Toole JF (eds). Handbook of Clinical Neurology. Elsevier Science, Amsterdam. 1989; 11: 233-254.
11. Taub NA, Wolfe CDA, Richardson E, Burney PGJ. Predicting the disability of first-time stroke sufferers at one year. Stroke. 1994; 25: 352-357.
12. Kwakkel G, Kollen BJ, Lindeman E. Understanding the pattern of functional recovery after stroke: Facts and theories. Restorative Neurology and Neuroscience. 2004; 22: 281-299.
13. Wagenaar RC, Emmerik REA. Relearning dynamics after stroke. In: Van der Kamp et al (eds). Movement disorders: Proceedings of the first symposium of the research institute for fundamental and clinical human movement sciences. Amsterdam. 1995, pages 51-77.
14. Wagenaar RC. Functional recovery after stroke. VU University Press, Amsterdam. 1990.
15. Tilling K, Sterne JAC, Wolfe CDA. Multilevel growth curve models with covariate effects: application to recovery after stroke. Statistics in Medicine. 2001; 20: 685-704.
16. Twisk JWR. Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis. European Journal of Epidemiology. 2004; 19: 769-776.
17. Twisk JWR. Applied longitudinal data analysis for epidemiology. Cambridge University Press. 2003.
18. Kwakkel G. Dynamics in functional recovery after stroke. Ponsen & Looijen BV, The Netherlands. 1998.
19. Kwakkel G, Wagenaar RC. Effect of duration of upper- and lower-extremity rehabilitation sessions and walking speed on recovery of interlimb coordination in hemiplegic gait. Physical Therapy. 2002; 82: 432– 448.
20. Shelton F, Reding, MJ. Effect of lesion location on upper limb motor recovery after stroke. Stroke. 2001; 32: 107-112.
21. Latash ML, Anson JG. What are "normal movements" in atypical populations? Behavioral and Brain Sciences. 1996; 19: 55-106.
22. Peppen van RPS, Kwakkel G, Wood-Dauphinee S, Hendriks HJM, Van der Wees PhJ, Dekker J. The impact of physical therapy on functional outcome after stroke: What's the evidence? Clinical Rehabilitation. 2004; 18: 833-862.

23. Hafsteinsdóttir TB, Algra A, Kappelle LJ, Grypdonck MH; Dutch NDT study group. Neurodevelopmental treatment after stroke: a comparative study. Journal of Neurology, Neurosurgery & Psychiatry. 2005; 76: 788-92.
24. Langhammer B, Stanghelle JK. Bobath or motor relearning programme? A comparison of two different approaches of physiotherapy in stroke rehabilitation: a randomized controlled study. Clinical Rehabilitation. 2000; 14: 361-369.
25. Bode RK, Heinemann AW, Semik P, Mallinson T. Relative importance of rehabilitation therapy characteristics on functional outcomes for persons with stroke. Stroke. 2004; 35: 2537–2542.

SUMMARY

This PhD thesis addresses the long term recovery of hemiplegic gait in severely affected stroke patients. It first reviews current rehabilitation research developments in functional recovery after stroke (chapter 2). This chapter provides background information for the research discussed in subsequent chapters. Thereafter, early and late stroke recovery was studied. Because of its non-linear nature and time-dependency, this required the establishment of acute, subacute and long term recovery profiles. This thesis therefore also includes a clinimetric and prognostic research section (chapters 3, 4, 5 and 6) and a section consisting of therapeutic intervention research (chapters 7 and 8) followed by a review discussing the possible mechanisms involved in functional recovery after stroke (chapter 9).

Chapter 2 reviews current rehabilitation research developments in functional recovery after stroke. With the institutionalization of stroke services across health care facilities a reduction in mortality rates, length of inpatient stay and improved independence in activities of daily living have been reported. Several systematic reviews show that traditional treatment approaches induce improvements that are confined to body function level only and do not generalize to a functional improvement level. Recently developed treatment strategies, that incorporate compensation strategies with a strong emphasis on functional training, may hold the key to optimal stroke rehabilitation. Intensity and task-specific exercise therapy are important components of such an approach. However, due to marked heterogeneity of the stroke population and poor methodological quality of many studies results are uncertain. Several options are discussed to overcome the problem of stroke heterogeneity in research designs.
Longitudinal repeated measurements designs are required to study the effects of non-linearity and time dependency of functional recovery in stroke. Furthermore, prognostic research based on sound clinimetric data generates relevant information that may guide the clinician in clinical decision making and in determining optimal treatment strategies. Guidelines assist the clinician in this responsibility.

Chapter 3 describes the relationship between 10 meter comfortable and maximum walking speed over time in the stroke population. The objective of this prospective cohort study was to identify the nature of this relationship (ie, fixed or dynamic). In addition, the significance of maximum walking speed and implications for the clinician are

addressed. As none of the stroke patients participating in this study was able to walk unassisted during the first week post-stroke onset and not all of the included 101 patients progressed to unassisted walking at some point in time, the findings were based on walking speed measurements from week 2 to week 52 in 81 patients. Walking speed progressively increased from the second to the fifty-second week within the comfortable speed measurements from .037 to .635 m/s and within the maximum speed measurements from .071 to .851 m/s. The overall mean comfortable and maximum speed was .472 and .638 m/s, respectively. The results of this study showed that in marked hemiplegic stroke patients maximum walking speed can be reliably estimated by comfortable walking speed time measurement converted to meters per second (m/s). It was found that maximum speed equals 1.32 times comfortable speed. Furthermore, this relation remained constant after adding co-variables to the regression model in an attempt to increase its precision, such as the patients' age, balance, hemiplegic arm and leg muscle strength and type of therapeutic intervention. In other words, the relationship between comfortable and maximum walking speed is fixed in post-stroke time in this stroke population. Based on this information, therapists can safely train stroke patients at (1.3 times) higher walking speeds in order to better prepare them for meeting the demands imposed by independent community living.

Chapter 4 describes the most robust variables in the early prediction of recovery of independent gait at 6 months in 101 stroke patients. Twenty-four determinants, possibly related to recovery of gait at 6 months, were measured within 14 days following stroke onset and onwards. Selection of variables was based on consistency in predicting outcome throughout the entire initial 10 week post-stroke period. This strategy was elected to identify predictive variables relative insensitive to the timing of post-stroke prediction. Bivariate logistic regression analysis produced a model that included patients' age, Motricity Index of arm and leg, Brunnstrom Fugl-Meyer of leg, Trunk Control Test, Barthel Index and type of intervention. Subsequently, a stepwise forward logistic regression statistical procedure was used for determining the probabilities of regaining independent gait. Moreover, sensitivity, specificity, accuracy, type I and II error and predictive value were calculated for model determinants. This study demonstrates that age and Barthel Index are the most robust variables within the first 10 week post-stroke months for predicting independent walking outcome at six months ie, lower age and higher Barthel index were associated with an increased probability of independent hemiplegic gait at 6 months. Odds ratios amounted to 0.9 for age and ranged from 1.4 to

1.7 for BI. In other words, each added year of age reduces the probability of regaining independent gait 0.9 times, while at the same time each higher BI point improves chances 1.4 to 1.7 times depending on the week of prediction.
However, predicting non-ambulatory patients within the initial weeks proved to be much more difficult. This finding implies that this logistic regression model is better suited for predicting ambulatory patients than non-ambulatory patients. Therefore, awareness of a too optimistic estimation of walking independence at six months is required when deciding on allocating post-stroke resources.
The accuracy of the model ranged between 75% and 86%. Sensitivity remained consistently high (ranging from 89% to 96%) and specificity moderately low (ranging from 53% to 62%) throughout the first 10 post-stroke weeks. Concomitant type I errors ranged from 37% to 47%, while type II errors ranged from 4% to 11%. Finally, predictive values ranged between 74% and 86%.

Chapter 5 discusses the longitudinal relationship between comfortable walking speed and Functional Ambulation Categories (FAC) scores for physically independent gait between week 4 and week 26 post-stroke onset in 73 patients. We initially determined whether repeated comfortable walking speed measurements were sensitive enough to detect post-stroke changes in physically independent gait in this severely affected stroke population and than proceeded by establishing the post-stroke time dependency of the relation between FAC scores for independent gait and comfortable walking speed measurement. In this study a minimal clinical important difference (MCID) of 10 percent was used as the minimal acceptable clinical change. Responsiveness ratios based on a 10 percent MCID exceeded the smallest detectable or real difference and ranged between 4.36 and 17.70. In particular within the 4th and 7th post-stroke week period, high responsiveness ratios were observed for comfortable walking speeds suggesting that relatively most relevant clinical walking speed changes took place within this period. These findings indicate that this instrument is sensitive to clinically important changes and suitable for demonstrating pretest-posttest time-related post-stroke changes in comfortable walking speed in our population. Based on random coefficient analysis, a significant 'between and within subject' regression coefficient of 0.113 (CI: 0.079 - 0.147, p = 0.000, count = 664) was demonstrated as well as significant negative interaction between time post-stroke measurement and FAC scores (b: -0.003, CI: -0.005 - - 0.001, p = 0.010). Over the entire study period, significant time dependent effects were demonstrated between walking speed and FAC scores for physically independent gait in that this relationship became weaker as post-stroke time passes (0.113 minus 0.003 for each consecutive measurement). Thus, this relation is subject to time related longitudinal changes. Subsequently, pretest-posttest walking speed differences and FAC agreement were determined. Here a pattern emerged of changing walking speeds coupled with high correlated FAC appraisals over time. There are indications that, in this relationship, repeated FAC appraisals are not only based on steady walking speeds, but that the walking speeds related to a specific FAC appraisal also change and, over time, may shift gradually from higher to lower speeds.

Chapter 6 describes the longitudinal relationship of functional change in walking ability and change in time-dependent covariates and presents a multivariate regression model for the prediction of longitudinal change of walking ability.
A prospective cohort study, based on 18 repeated measurements over time during the first post-stroke year, was conducted in 101 acute stroke patients with first-ever ischemic middle cerebral artery strokes. Baseline characteristics as well as longitudinal information from Functional Ambulation Categories (FAC), Fugl-Meyer leg score (FM-leg), Motricity leg score (MI-leg), letter cancellation task (LCT), Fugl-Meyer balance score (FM-balance) and timed-balance test (TBT) were obtained. Intervention consisted of a basic rehabilitation programme with additional arm, leg or air splint therapy. Change scores on the Functional Ambulation Categories (FAC) over time constituted outcome.
In total 1532 of the 1717 change scores were available for random coefficient analysis. In the final model improvement in the TBT change scores was the most important factor in predicting improvement on FAC (β=0.094) followed by changes scores on FM-leg (β=0.014), LCT omissions (β=-0.010) and MI leg test (β=0.001). In addition, time itself was significantly negatively associated with improvement in walking ability (β=-0.002). It is concluded that in order to achieve improvement in walking ability improvement in standing balance control is more important than improvement in leg strength or synergism, whereas reduction in visuo-spatial inattention is independently related to improvement of gait. Finally, time itself is an independent covariate which is negatively associated with change on FAC suggesting that most pronounced improvements occur early after stroke onset.

Chapter 7 describes a pilot study aimed to investigate the carry-over effects on comfortable walking speed after overloading the lower hemiparetic extremity in chronic stroke patients. It was hypothesized that overloading the hemiparetic lower extremity would generate increased motor output resulting in carry-over effects. In some sports these effects are commonly used in order to improve performance. A single subject research study was conducted using a withdrawal design (A-B-A-B-A) on three patients with ischemic middle cerebral artery infarction. Chronic stroke patients (≥ 3 years post-stroke) were recruited with stage 3 or 4 Fugl-Meyer scores in the lower extremity and the ability to ambulate independently without walking aids. Based on this withdrawal design, the daily procedure included walking at comfortable speeds 5 times 10 meters during the A_1 phase and 3 times 10 meters during all subsequent phases. This procedure was repeated for five consecutive days. Two lbs (B_1) and 6 lbs (B_2) weight cuffs were attached to the distal lower hemiparetic extremity and randomized over the two B phases. Control (A_1, A_2, A_3) and intervention (B_1, B_2) phases were alternated with brief resting periods. Mean comfortable walking speed for 10 meters constituted the outcome variable. All patients showed significant differences between phases ($\chi^2 = 34.187$; $p < 0.001$). However, with the exception of a carry-over effect between the A_1 (0.86 m/sec) and A_2 (0.89 m/sec) phases in one subject ($p = 0.043$), no significant carry-over effects were found on ensuing A_2 and A_3 control phases. Although gradual improvements in comfortable walking speed between subsequent days were found, the present pilot study did not demonstrate favourable group effects on comfortable walking speed as a result of limb overloading.

Chapter 8 discusses a study conducted to assess the long term effects at 1 year after stroke in patients who participated in an upper and lower limb intensity training programme in the acute and subacute rehabilitation phases. A three group randomised controlled trial with repeated measures was used. One hundred and one patients with a primary middle cerebral artery stroke were randomly allocated to one of three groups for a 20 week rehabilitation programme with emphasis on (1) upper limb function, (2) lower limb function or (3) immobilisation with an inflatable pressure splint (control group). Follow-up assessments within and between groups were compared at 6, 9, and 12 months after stroke. Outcome was based on several ADL and quality of life measures. No statistically significant effects were found for treatment assignment from 6 months onwards. At a group level, the significant differences in efficacy demonstrated at 20 weeks after stroke in favour of the lower limb remained. However, no significant differences in functional recovery between groups were found for Barthel Index (BI), Functional Ambulation Categories (FAC), Action Research Arm Test (ARAT), comfortable and maximal walking speed, Nottingham Health Profile part 1(NHP-part 1), Sickness

Impact Profile-68 (SIP-68), and Frenchay Activities Index (FAI) from 6 months onwards. At an individual subject level a substantial number of patients showed improvement or deterioration in upper limb function (n=8 and 5, respectively) and lower limb function (n=19 and 9, respectively). Activities of daily living (ADL) scores showed that five patients deteriorated and four improved beyond the error threshold from 6 months onwards. In particular, patients with some but incomplete functional recovery at 6 months are likely to continue to improve or regress from 6 months onwards.
It was concluded that on average patients maintained their functional gains for up to 1 year after stroke after receiving a 20 week upper or lower limb function training programme. However, a significant number of patients with incomplete recovery showed improvements or deterioration in dexterity, walking ability, and ADL beyond the error threshold.

Chapter 9 reflects on the facts and theories in relation to the understanding of the pattern of functional recovery after stroke. Longitudinal studies show that almost all stroke patients experience at least some predictable degree of functional recovery in the first six months post-stroke. However, the non-linear pattern as a function of time is not well understood. Several mechanisms are presumed to be involved, such as recovery of penumbral tissues, neural plasticity, resolution of diaschisis and behavioural compensation strategies. Rehabilitation is believed to modulate this logistic pattern of recovery, probably by interacting with these underlying processes. However, prediction models that are adjusted for the effects of time after stroke onset suggest that outcome is largely defined within the first weeks post-stroke, although functional improvement has been found to extend beyond six months post-stroke. In addition, kinematic studies show that functional improvement is more than recovery from impaired body functions alone, suggesting that patients are able to improve in terms of gait or dexterity deficits using behavioural compensation strategies. Therefore, understanding the impact of task-dependent cortical activation patterns in non-invasive methods requires not only information derived from longitudinal studies pertaining to functional outcomes, but also a better understanding of what is kinematically learned during the acquisition of new skills.

Chapter 10 summarizes the main conclusions from this thesis, discusses implications and perspectives and provides recommendations for future research. It stresses the need for further prognostic research based on repeated measurements and cross-sectional and longitudinal statistical analysis. It discusses the problem of heterogeneity of the stroke population and addresses relevant methodological issues in clinical stroke research.

SAMENVATTING

Dit proefschrift richt zich op de bestudering van het lange termijn herstel van loopvaardigheid bij patiënten met een ernstig cerebro-vasculair accident (CVA). In het tweede hoofdstuk worden recente ontwikkelingen beschreven op het gebied van revalidatieonderzoek t.a.v. van het functionele herstel na een CVA. Dit hoofdstuk geeft achtergrondinformatie voor het promotieonderzoek. Hierna wordt zowel het vroege als late herstel beschreven. Vanwege het non-lineaire beloop en de tijdsafhankelijkheid van dit herstel werden acute, subacute en lange termijn herstelprofielen bestudeerd. Dit proefschrift is derhalve opgebouwd uit een klinimetrisch en een prognostisch deel (Hoofdstukken 3, 4, 5 en 6) en uit een therapeutisch interventie deel (Hoofdstukken 7 en 8) gevolgd door een bespreking van de mogelijke mechanismen die een rol spelen bij het functionele herstel na een CVA (Hoofdstuk 9).

Hoofdstuk 2 beschrijft de huidige stand van kennis over het functionele herstel na een beroerte gegeneerd door revalidatieonderzoek. Door de introductie van zogenaamde stroke services in de zorgketen zijn de mortaliteit, opnameduur en afhankelijkheid van de patiënt verminderd. Diverse systematische reviews tonen aan dat de effecten van de traditionele behandelingsmethoden zich beperken tot het niveau van lichaamsfuncties en niet generaliseren naar het functionele niveau. Meer recent ontwikkelde behandelstrategieën met een sterk accent op functionele training vervullen een belangrijke rol bij het verwezenlijken van optimale revalidatie van de CVA patiënt. Daarin spelen intensiteit en taakspecificiteit een belangrijke rol. Vanwege de uitgesproken heterogeniteit van de CVA populatie en onvoldoende methodologische kwaliteit van veel studies zijn de gerapporteerde resultaten veelal onzeker.
In dit hoofdstuk worden verschillende opties besproken om het probleem van de heterogeniteit van de studiepopulatie het hoofd te bieden. Herhaald in de tijd uitgevoerde metingen zijn nodig om de effecten van non-ineariteit en tijdsafhankelijkheid van het functionele herstel na een CVA te bestuderen. Prognostische studies, die gebaseerd zijn op solide klinimetrische gegevens, leveren informatie op die van belang is voor klinische besluitvorming en het bepalen van optimale behandelstrategieën. Behandelrichtlijnen ondersteunen de clinicus en therapeut in het revalidatieproces.

Hoofdstuk 3 beschrijft de relatie in de tijd tussen 10 meter comfortabele en maximale loopsnelheid in de CVA populatie. Het doel van dit prospectieve cohort onderzoek was de aard van deze relatie vast te stellen (d.w.z. vast of dynamisch). Bovendien worden in dit hoofdstuk het belang van maximale loopsnelheid en de klinische implicaties besproken. Omdat in dit onderzoek geen van de deelnemende patiënten zelfstandig loopvaardig was in de eerste week na het CVA en bovendien niet alle 101 geïncludeerde patiënten deze status bereikten op enig moment na het CVA, waren de bevindingen gebaseerd op loopsnelheidmetingen in de periode tussen de 2de en 52ste week bij 81 patiënten. De comfortabele loopsnelheid nam geleidelijk toe tussen de 2de en 52ste week van .037 tot .635 m/s. De maximale loopsnelheid gaf een soortgelijk beeld te zien en nam toe van .071 tot .851 m/s, terwijl de gemiddelde comfortabele en maximale loopsnelheden respectievelijk .472 m/s en .638 m/s bedroegen. De resultaten van dit onderzoek laten zien dat bij hemiplegische CVA patiënten op basis van comfortabele loopsnelheidmetingen de maximale loopsnelheid betrouwbaar kan worden voorspeld, d.w.z. de maximale loopsnelheid komt overeen met 1.32 keer de comfortabele loopsnelheid. Deze relatie werd niet beïnvloed door het toevoegen van co-variabelen (d.w.z. leeftijd van de patiënt, evenwicht, spierkracht in hemiplegische arm en been en type interventie) aan het regressiemodel in een poging om de precisie van deze associatie te verbeteren. Met andere woorden deze relatie tussen comfortabele en maximale loopsnelheid blijft constant in de tijd na een CVA in onze populatie. Op basis van deze informatie kunnen fysiotherapeuten CVA patiënten beter voorbereiden op de periode na ontslag door veilig (tot 1.3 keer) hogere loopsnelheden te oefenen.

Hoofdstuk 4 beschrijft de meest robuuste vroege voorspellende variabelen voor het herstel van het onafhankelijk looppatroon op 6 maanden na een CVA bij 101 patiënten. Vierentwintig determinanten, die mogelijk gerelateerd waren aan het herstel van loopvaardigheid na een CVA, werden binnen twee weken en daarna geregistreerd. De selectie van de variabelen vond plaats op basis van hun vermogen om iedere week de uitkomst te kunnen prediceren gedurende eerste 10 weken na een CVA. Er is voor deze strategie gekozen om zodoende variabelen te selecteren die relatief ongevoelig zijn voor het tijdstip van predictie na een CVA. Bivariate logistische regressie analyse leverde een model op met de volgende variabelen: leeftijd van patiënt, Motricity Index van hemiplegische arm en been, Brunnstrom Fugl-Meyer van hemiplegisch been, Trunk Control Test, Barthel Index (BI) en type interventie. Vervolgens is op basis van een 'stepwise forward' logistische regressie statistische procedure de kans berekend op het ontwikkelen van onafhankelijke loopvaardigheid na 6 maanden. Bovendien werd criterium validiteit vastgesteld door sensitiviteit, specificiteit, accuratesse, type I en II fouten en voorspellende waarden te berekenen voor de in het model opgenomen variabelen. Dit onderzoek toont aan dat leeftijd en BI de meest robuuste variabelen zijn binnen de eerste 10 weken na een CVA die een zelfstandig looppatroon na 6 maanden kunnen voorspellen, d.w.z. een lagere leeftijd en hogere Barthel Index zijn geassocieerd met een verhoogde kans op het bereiken van een zelfstandig looppatroon na 6 maanden. Odds ratio's bedroegen 0.9 voor leeftijd en varieerden van 1.4 tot 1.7 voor BI. Met andere woorden elk extra leeftijdsjaar vermindert de kans op zelfstandig lopen met een factor 0.9, terwijl tegelijkertijd elk extra BI punt de kans doet toenemen met 1.4 tot 1.7 keer afhankelijk van de week waarin de meting heeft plaatsgevonden. Het voorspellen binnen de eerste 10 weken van CVA patiënten die niet loopvaardig worden bleek echter veel moeilijker te zijn. Deze bevinding leidt tot de conclusie dat het logistisch regressie model beter geschikt is om de aanwezigheid dan de afwezigheid van loopvaardigheid bij CVA patiënten na 6 maanden te voorspellen. Het gevolg hiervan kan zijn dat op basis van een te optimistische inschatting verstrekking van hulpmiddelen etc. plaats vindt. De accuratesse van het model varieerde van 75 tot 86 procent. Sensitiviteit bleef constant hoog (89% - 96%) terwijl specificiteit lager (53% - 62%) uitviel binnen de eerste 10 weken na een CVA. De hiermee samenhangende type I fouten varieerden van 37 tot 47 procent, terwijl type II fouten varieerden van 4 tot 11 procent. De voorspellende waarden varieerden tussen 74 en 86 procent.

Hoofdstuk 5 behandelt de longitudinale relatie tussen comfortabele loopsnelheid en Functional Ambulation Categories (FAC) classificatie voor een fysiek zelfstandig looppatroon in de periode tussen de vierde en zesentwintigste week na een CVA bij 73 patiënten. In eerste instantie werd de aandacht gericht op de beantwoording van de vraag of herhaalde comfortabele loopsnelheidmetingen sensitief genoeg waren om veranderingen in het looppatroon na een CVA te kunnen detecteren. Aansluitend werd de tijdsafhankelijkheid in de relatie tussen FAC scores voor een onafhankelijk looppatroon en comfortabele loopsnelheidmetingen na een CVA vastgesteld. Hierbij werd voor het aantonen van een minimaal acceptabele klinische verandering een minimaal klinisch relevant verschil (MCID) van 10 procent gehanteerd. Responsiveness ratio's gebaseerd op een MCID van 10% overtroffen de kritische waarde van 1.96 (kleinst waarneembaar verschil) en varieerden van 4.36 tot 17.70. In het bijzonder werden in de periode tussen de vierde en zevende week na het CVA hoge responsiveness ratio's waargenomen voor comfortabele loopsnelheid hetgeen erop wijst dat binnen deze periode relatief de meeste klinische veranderingen in loopsnelheid plaatsvonden. Deze bevindingen geven aan dat

dit instrument gevoelig is voor het meten van klinische belangrijke veranderingen en geschikt om tijdsafhankelijke veranderingen tussen voor- en nametingen bij comfortabele loopsnelheden aan te tonen in onze CVA populatie.
Tevens werd op basis van een random coefficient analyse een significante ‘intra- en intersubject’ regressiecoëfficiënt van 0.113 (CI: 0.079 - 0.147, p = 0.000, aantal = 664) gevonden en bovendien een significante negatieve interactie (b: -0.003, CI: -0.005 - -0.001, p = 0.010) waargenomen tussen het tijdstip van meting na een CVA en FAC scores. Gedurende de gehele meetperiode werden tijdsafhankelijke effecten aangetoond tussen loopsnelheid en FAC scores voor het fysiek zelfstandig looppatroon, waarbij deze associatie zwakker werd bij achtereenvolgende metingen. Vervolgens zijn veranderingen in loopsnelheden tussen voor- en nametingen en de mate van overeenstemming in FAC scores tussen voor- en nametingen vastgesteld, waarbij een patroon zichtbaar werd van veranderende loopsnelheden gekoppeld aan hoog gecorreleerde FAC scores in de tijd. Er zijn aanwijzingen dat in deze relatie de FAC scores niet alleen gebaseerd zijn op stabiele loopsnelheden maar dat de loopsnelheden die gerelateerd zijn aan een specifieke FAC score ook onderhevig zijn aan veranderingen en dat in de tijd deze snelheden geleidelijk afnemen.

Hoofdstuk 6 beschrijft de longitudinale relatie tussen functionele veranderingen in loopvaardigheid en veranderingen die optreden bij tijdsafhankelijke covariaten. Op basis van een multivariaat multi-level regressie model werden de longitudinale veranderingen in loopvaardigheid voorspeld.
Een prospectief cohort studie, gebaseerd op 18 herhaalde metingen in de tijd gedurende het eerste jaar, werd verricht bij 101 patiënten met een ischaemisch CVA van de arteria cerebri media. Informatie werd verkregen van tijdsonafhankelijke variabelen en uit tijdsafhankelijke longitudinale metingen van Functional Ambulation Categories (FAC), Fugl-Meyer been scores (FM-leg), Motricity been scores (MI-leg), letter cancellation task (LCT), Fugl-Meyer balans scores (FM-balance) and timed-balance test (TBT). De behandeling bestond uit een regulier revalidatie programma met daaraan toegevoegd extra arm-, been- of airsplinttherapie. De veranderscores van de Functional Ambulation Categories (FAC) in de tijd bepaalden de uitkomstmaat.
In totaal waren 1532 van de 1717 veranderscores beschikbaar voor random coefficient analyse. In het eindmodel bleken verbeteringen in TBT veranderscores de belangrijkste voorspellende factoren te zijn voor verbeteringen in FAC (β=0.094) gevolgd door veranderscores FM-been (β=0.014), LCT omissies (β=-0.010) en MI been (β=0.001).

Bovendien bleek de factor tijd zelf significant en negatief geassocieerd te zijn met verbeteringen in loopvaardigheid (β=-0.002).
Er werd geconcludeerd dat voor het bereiken van verbeteringen in loopvaardigheid verbeteringen van het evenwicht in stand belangrijker zijn dan verbeteringen in spierkracht van het been of synergisme, terwijl een afname in visuo-spatiële inattentie onafhankelijk gerelateerd is aan verbeteringen in loopvaardigheid. Tot slot blijkt tijd na een CVA zelf een onafhankelijke covariaat te zijn, die negatief geassocieerd is met veranderingen op de FAC, hetgeen er op wijst dat de meest uitgesproken verbeteringen vroeg na het ontstaan van een CVA optreden.

Hoofdstuk 7 beschrijft een pilot studie naar de 'carry-over' effecten van verzwaring van het hemiplegische been op de comfortabele loopsnelheid bij chronische CVA patiënten. Hierbij was de achterliggende gedachte dat verzwaring van het hemiplegische been zou leiden tot een toename van motorische output en dientengevolge tot 'carry-over' effecten. Bij sommige sporten wordt hiervan gebruikt gemaakt om de uitvoering en prestatie te verbeteren. Een 'single subject design' onderzoek werd uitgevoerd op basis van 'withdrawal' (A-B-A-B-A) bij drie patiënten met een ischaemisch infarct van de arteria cerebri media. Patiënten (≥ 3 jaar na CVA) met stadium 3 of 4 op de Fugl-Meyer schaal in de onderste extremiteit, die in staat waren om zonder hulpmiddel zelfstandig te lopen, werden gerekruteerd. Op basis van het 'withdrawal' concept werden bij het lopen dagelijkse metingen verricht van comfortabele snelheden gedurende 5 keer 10 meter tijdens de A_1 fase en 3 keer 10 meter tijdens alle volgende fasen. Deze procedure werd herhaald gedurende vijf achtereenvolgende dagen. Twee lbs (B_1) en 6 lbs (B_2) verzwaringen werden aangebracht aan de distale hemiplegische onderste extremiteit en gerandomiseerd over de twee B fasen. Controle (A_1, A_2, A_3) en interventie (B_1, B_2) fasen werden afgewisseld met korte rustperioden. De gemiddelde loopsnelheid over 10 meter was hierbij de uitkomstvariabele. Alle patiënten lieten significante veranderingen zien tussen fasen ($\chi^2 = 34.187$; $p < 0.001$). Met uitzondering van een 'carry-over' effect tussen de A_1 (0.86 m/sec) en A_2 (0.89 m/sec) fasen bij één persoon ($p = 0.043$) werden er geen significante 'carry-over' effecten waargenomen tussen opeenvolgende A_2 en A_3 controle fasen. Hoewel geleidelijke verbeteringen in de comfortabele loopsnelheid tussen opeenvolgende dagen werden aangetoond konden in dit onderzoek geen gunstige groepeffecten worden vastgesteld ten gevolge van verzwaring van het hemiplegisch been.

Hoofdstuk 8 bespreekt een studie die is uitgevoerd om de lange termijn effecten na één jaar te beoordelen bij CVA patiënten die hebben deelgenomen aan een intensief arm- en beenoefenprogramma welke zij ondergingen in de acute en subacute revalidatie fase.
Een gerandomiseerd gecontroleerd onderzoek gebaseerd op herhaalde metingen in de tijd werd uitgevoerd. Honderd en één patiënten met een primaire CVA ten gevolge van een arteria cerebri media infarct werden random toegewezen aan één van drie groepen voor het volgen van een revalidatieprogramma gedurende 20 weken. Deze groepen kregen revalidatie met nadruk op de bovenste extremiteit (groep 1), onderste extremiteit (groep 2) en immobilisatie van beide hemiplegische extremiteiten met een opblaasbare druksplint (controle groep 3). De informatie verkregen uit de herhaalde metingen werd vergeleken tussen en binnen groepen na 6, 9 en 12 maanden. De uitkomst was gebaseerd op diverse meetinstrumenten die betrekking hebben op Activiteiten van het Dagelijks Leven (ADL) en kwaliteit van leven. Er werden geen statistisch significante effecten gevonden tussen de groepen vanaf 6 maanden na het CVA. Op groepsniveau persisteerden de significante effecten in doeltreffendheid, welke werden waargenomen bij de twintigste week na CVA, voor de onderste extremiteit. Er werden echter geen significante effecten gevonden ten aanzien van het functionele herstel voor de BI, FAC, Action Research Arm Test (ARAT), comfortabele en maximale loopsnelheid, Nottingham Health Profile deel 1 (NHP-deel 1), Sickness Impact Profile-68 (SIP-68) en Frenchay Activities Index (FAI) vanaf 6 maanden na een CVA. Op patiëntniveau werd bij een substantieel aantal patiënten verbeteringen en verslechteringen waargenomen in armfunctie (respectievelijk 8 en 5) en beenfunctie (respectievelijk 19 en 9). Gebaseerd op ADL scores was er een verslechtering bij vijf en een verbetering bij 4 patiënten te zien vanaf 6 maanden. In het bijzonder gaven patiënten, die onvolledig hersteld waren, veranderingen te zien in handvaardigheid, loopvaardigheid en ADL.
Geconcludeerd werd dat, op basis van het arm- en beenoefenprogramma dat werd uitgevoerd gedurende de eerste 20 weken na het CVA, gemiddeld beschouwd de onderzochte patiënten hun functionele verbeteringen handhaafden tot één jaar na de CVA. Bij een significant aantal patiënten met onvolledig herstel werden verbeteringen of verslechteringen in handvaardigheid, loopvaardigheid en ADL aangetroffen.

Hoofdstuk 9 gaat in op de feiten en theorieën die van belang zijn bij de begripsvorming ten aanzien van functionele herstelpatronen na een CVA. Longitudinale studies tonen aan dat bijna alle CVA patiënten tenminste enig voorspelbaar functioneel herstel doormaken binnen de eerste 6 maanden. Het niet-lineaire herstelpatroon als functie van tijd wordt evenwel niet goed begrepen. Diverse mechanismen zijn mogelijk hierbij betrokken, zoals het herstel van penumbral parachym, neurale plasticiteit, diaschisis en compensatoir gedrag. Naar verwachting moduleert revalidatie dit logistische herstel patroon, waarschijnlijk door interactie met onderliggende processen. Predictiemodellen, die rekening houden met het tijdseffect na een CVA, laten zien dat dit herstel vooral plaatsvindt binnen de eerste weken na een CVA. Bekend is echter dat functioneel herstel soms 6 maanden na een CVA ook nog kan optreden. Kinematische studies tonen aan dat functioneel herstel meer behelst dan alleen het herstel van lichaamsfuncties hetgeen erop wijst dat patiënten in staat zijn op basis van het toepassen van compensatoir gedrag verbeteringen te genereren in het looppatroon en de handvaardigheid. Het inzicht krijgen in taakafhankelijke corticale activatie patronen met behulp van non-invasieve onderzoeksmethoden vereist naast informatie over het functionele herstel uit longitudinale studies ook een beter begrip van wat precies kinematisch wordt geleerd tijdens het aanleren van nieuwe vaardigheden.

Hoofdstuk 10 geeft een overzicht van de belangrijkste conclusies van de in dit proefschrift beschreven studies en bespreekt de implicaties en perspectieven naast de aanbevelingen voor vervolgonderzoek. Het benadrukt het belang van aanvullend prognostisch longitudinaal onderzoek. Het bespreekt ook het heterogeniteitprobleem binnen de CVA populatie en methodologische problemen welke zich voordoen bij klinisch onderzoek na een CVA.

PUBLICATIONS

International journals

Kwakkel G, Kollen BJ, Twisk J. Impact of time on improvement of outcome after stroke: A longitudinal prospective study. Stroke. 2006; 37: 2348-2353.

Kollen BJ, Kwakkel G, Lindeman E. Time dependency of walking classification in stroke. Physical Therapy. 2006; 86: 618-625.

Kollen BJ, Kwakkel G, Lindeman E. Hemiplegic gait after stroke: Is measurement of maximum speed required? Archives of Physical Medicine and Rehabilitation. 2006; 87: 358-363.

Arabin B, Roos C, Kollen BJ, Eyck van J. Comparison of transvaginal sonography in a recumbent and standing position to predict spontaneous preterm birth in singleton and twin pregnancies. Ultrasound in Obstetrics and Gynecology. 2006; 27: 377-386.

Kollen BJ, Kwakkel G, Lindeman E. Longitudinal robustness of variables predicting independent gait after severe middle cerebral artery stroke: A prospective cohort study. Clinical Rehabilitation. 2006; 20: 262-268.

Kollen BJ, Kwakkel G, Lindeman E. Functional recovery after stroke: A review of current developments in stroke rehabilitation research. Reviews on Recent Clinical Trials. 2006; 1 (1): 75-80.

Kollen BJ, Port van de I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke: A longitudinal prospective study. Stroke. 2005; 36: 2676-2680.

Kwakkel G, Kollen BJ, Lindeman E. Understanding the pattern of functional recovery after stroke: Facts and theories. Restorative Neurology and Neuroscience. 2004; 22: 281-299.

Kwakkel G, Kollen BJ, Grond van der J, Prevo AJH. Probability of regaining dexterity in the flaccid upper limb: Impact of severity of paresis and time since onset in acute stroke. Stroke. 2003; 34: 2181-2186.

Kwakkel G, Kollen BJ, Wagenaar RC. Long term effects of intensity of arm and leg training in stroke patients: A randomised trial. Journal of Neurology, Neurosurgery and Psychiatry. 2002; 72: 474-480.

Kollen BJ, Rietberg MB, Kwakkel G, Emmelot CH. Effects of overloading of the lower hemiparetic extremity on walking speed in stroke patients: A pilot study. NeuroRehabilitation. 2000; 14 (3): 159-164.

Kwakkel G, Kollen BJ, Wagenaar RC. Therapy impact on functional recovery in stroke rehabilitation - A critical review of the literature. Physiotherapy. 1999; 85 (7): 377-391.

Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ. Predicting disability in stroke - A critical review of the literature. Age and Ageing. 1996; 25: 479-489.

Dutch journals

Baarveld F, Boendermaker P, Heule G, Kollen BJ. Effect van onderwijs over knie-, enkel- en onderbeenproblemen bij eerstejaarse huisartsen in opleiding. Tijdschrift voor Medisch Onderwijs. 2005; 24 (6): 245-249.

Baarveld F, Kollen BJ. Behandeling van niet-acute sportgerelateerde problemen van de onderste extremiteit in de eerste lijn door de fysiotherapeut. Nederlands Tijdschrift voor Fysiotherapie. 2004; 114 (6): 150-153.

Peppen van RPS, Harmeling – van der Wel BC, Kollen BJ, Hobbelen JSM, Buurke JH, Halfens J, Wagenborg L, Vogel MJ, Berns M, Klaveren van R, Hendriks HJM, Heldoorn M, Wees van der PhJ, Dekker J, Kwakkel G. Effecten van fysiotherapeutische interventies bij patiënten met een beroerte: Een systematisch literatuuronderzoek. Nederlands Tijdschrift voor Fysiotherapie. 2004; 114 (5): 126-153.

Peppen van RPS, Kwakkel G, Harmeling – van der Wel BC, Kollen BJ, Hobbelen JSM, Buurke JH, Halfens J, Wagenborg L, Vogel MJ, Berns M, Klaveren van R, Hendriks HJM, Dekker J. KNGF–richtlijn beroerte. Nederlands Tijdschrift voor Fysiotherapie Supplement. 2004; 114 (5): 3-78.

Kwakkel G, Mulder FV, Ooms AC, Kollen BJ. Het prediceren van loopvaardigheid na een beroerte: Een prospectief cohort onderzoek. Nederlands Tijdschrift voor Fysiotherapie. 2004; 114 (1): 2-8.

Kwakkel G, Kollen BJ. Eerst analyseren, dan meten: De rol van het NDT concept in effectonderzoek nader beschouwd. Nederlands Tijdschrift voor Fysiotherapie. 2001; 111 (5): 125-130.

Kwakkel G, Kollen BJ, Wagenaar RC. Dynamica van het functionele herstel van CVA-patiënten: Effecten van bewegingstherapie nader geanalyseerd. Nederlands Tijdschrift voor Fysiotherapie. 2001; 111 (1): 13-21.

Kollen BJ. SOAP en het neurologisch onderzoek. Fysiotherapie en Ouderenzorg. 1997; 12 (2): 17-24.

Kollen BJ, Kwakkel G. De pathofysiologie van spasticiteit IV - Principes en effecten van fysiotherapeutische interventies op spasticiteit. Een kritisch overzicht. Nederlands Tijdschrift voor Fysiotherapie. 1995; 105 (5): 144-159.

Kollen BJ. Revalidatie na een beroerte. Nederlands Tijdschrift voor Fysiotherapie. 1985; 95 (7/8): 151-155.

Kollen BJ. (Facilitatie of Inhibitie) Fysiotherapie bij de volwassen hemiplegie patiënt. Nederlands Tijdschrift voor Fysiotherapie. 1982; 92 (10): 226-260.

Kollen BJ. Fysiotherapie bij de lumbale H.N.P. Tijdschrift voor Geneesmiddelen Onderzoek. 1980; 5 (2): 637-645.

Kollen BJ. Het cerebellair syndroom. Nederlands Tijdschrift voor Fysiotherapie. 1979; 89 (6): 138-145.

Steen van der A, Kollen BJ. Hernia nuclei pulposi op lumbosacraal niveau. Nederlands Tijdschrift voor Fysiotherapie. 1979; 89 (3): 52-55.

DANKWOORD

Ik ben veel dank verschuldigd aan mijn promotor en copromotor die mij de gelegenheid boden om dit project aan te gaan en te volbrengen.
Prof. Dr. E. Lindeman, verbonden aan de Universiteit Utrecht, was bereid dit promotieonderzoek te begeleiden. Beste Eline, vanwege mijn status als 'externe' promovendus heeft deze begeleiding voor een belangrijk deel langs electronische weg plaatsgevonden. Ik heb daarbij jouw professionele en persoonlijke aanpak bijzonder gewaardeerd. De ruimte die ik kreeg om invulling te geven aan dit onderzoek heb ik als zeer stimulerend ervaren. Jouw commentaar hield mij bij de les.
Dr. G. Kwakkel bood mij de gelegenheid om op basis van zijn - met veel zorg en inspanning verkregen - data dit promotieonderzoek te verrichten. Beste Gert, jouw wetenschappelijke onderbouwing van wat nu neuro-revalidatie wordt genoemd heeft je gemaakt tot een autoriteit op dit gebied. Onze samenwerking, die al dateert van het begin van de tachtiger jaren en geleid heeft tot veel publicaties, was en is goed vooral vanwege onze gemeenschappelijke interesse in deze materie en enthousiasme om hieraan meer evidentie toe te voegen. Ik heb de geboden gelegenheid om dit promotieonderzoek uit te voeren erg op prijs gesteld, heb dankbaar gebruik gemaakt van jouw omvangrijke kennis op dit gebied en hoop dat onze samenwerking niet ophoudt na voltooiing van dit project.
De leden van de beoordelingscommissie, Prof. dr. A. Algra, Prof. dr. P.J.M. Helders, Prof. dr. H.C.W. de Vet, Prof. dr. D.T. Wade en Prof. dr. J.H.J. Wokke, wil ik danken voor de bereidheid het manuscript grondig te bestuderen en kritisch te beschouwen.

Daarnaast wil ik Pim Gelderman, Steffen Zanen, Kees Emmelot, Irma van Straaten, Klaas Groenier en Frank Baarveld bedanken voor al hun aanmoedigingen en goede adviezen, Mia Kollen voor het kritisch doorlezen van de Nederlandse samenvatting en Thea Bakker van de stafdienst Zorgopleiding en Onderzoek voor de getoonde interesse en het begrip voor mijn preoccupatie, ook tijdens kantooruren, met dit voor mij zo belangrijk onderzoek. Voorts wil ik mijn collega Helen Klip hartelijk bedanken voor haar inspirerende adviezen en waardevolle bijdrage aan de goede afloop van dit project.

Ten slotte wil ik mijn broer Fred bedanken voor de voortreffelijke wijze waarop hij mij tijdens de studie epidemiologie en daarna heeft ondersteund. Fred, jij bent als oudere broer in menig opzicht mijn voorbeeld geweest, vooral wat betreft werkethos, doorzettingsvermogen en doelgerichtheid. Deze eigenschappen komen zeer goed van pas bij het uitvoeren en afronden van promotieonderzoek. Helaas komt deze promotie voor onze ouders en broer Hans veel te laat.

CURRICULUM VITAE

De schrijver van dit proefschrift bracht zijn jeugd, inclusief middelbare school en studie fysiotherapie, door in Amsterdam. In 1976 volgde een aanstelling op de afdeling fysiotherapie van de Valeriuskliniek in Amsterdam (destijds een neurologisch, neurochirurgisch en psychiatrisch ziekenhuis). Van 1980 tot en met 1983 was hij hoofd van deze afdeling.

Vanaf 1983 vervolgde hij zijn loopbaan als fysiotherapeut in Canada. In Toronto was hij eerst verbonden aan St. Michael's Hospital en daarna, vanaf 1986, aan Baycrest Centre for Geriatric Care. Na terugkomst in Nederland in 1989 werd het Sophia Ziekenhuis te Zwolle (en na de fusie de Isala klinieken) zijn nieuwe werkgever. Vanaf 2002 volgde hij postinitieel masteronderwijs epidemiologie aan de Vrije Universiteit in Amsterdam en rondde deze opleiding in 2004 af met de graad 'Master Epidemiologie'. In 2004 was hij tijdelijk gedetacheerd als onderzoeker bij de disciplinegroep Huisartsgeneeskunde van de Rijksuniversiteit Groningen.

Thans is hij werkzaam op het Research Bureau van de Isala klinieken waar hij toegepast wetenschappelijk patiëntgebonden onderzoek ondersteunt. Voorts is hij als methodoloog verbonden aan de lokale medisch ethische toetsingscommissie.